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         JUN 13
                 USPATFULL and USPAT2 updated with 11-character
                 patent numbers for U.S. applications
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         JUN 30 STN AnaVist enhanced with database content from EPFULL
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         JUL 28 CA/CAplus patent coverage enhanced
NEWS 18 JUL 28 EPFULL enhanced with additional legal status
                 information from the epoline Register
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         JUL 28 IFICDB, IFIPAT, and IFIUDB reloaded with enhancements
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NEWS 22 AUG 13 CA/CAplus enhanced with printed Chemical Abstracts
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                 CAOLD to be discontinued on December 31, 2008
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         AUG 25
                 CA/CAplus, CASREACT, and IFI and USPAT databases
                 enhanced for more flexible patent number searching
NEWS 26 AUG 27
                 CAS definition of basic patents expanded to ensure
                 comprehensive access to substance and sequence
                 information
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```
chain nodes :
10 11 20 21 22 23
ring nodes :
1 2 3 4 5 14 15 16 17 18 19 24
chain bonds :
2-18 4-10 10-11 15-20 20-21 20-22 22-23
ring bonds :
1-2 \quad 1-5 \quad 2-3 \quad 3-24 \quad 4-5 \quad 4-24 \quad 14-15 \quad 14-19 \quad 15-16 \quad 16-17 \quad 17-18 \quad 18-19
exact/norm bonds :
1-2 \quad 1-5 \quad 2-3 \quad 2-18 \quad 3-24 \quad 4-10 \quad 4-5 \quad 4-24 \quad 10-11 \quad 20-21 \quad 20-22 \quad 22-23
exact bonds :
15-20
normalized bonds :
14-15 14-19 15-16 16-17 17-18 18-19
isolated ring systems :
containing 1 :
```

G1:C,N

G2:Ak, NH2, NO2

G3:0

G4

G5:C, N, Zn, H

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 10:CLASS 11:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom 20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:Atom

L1 STRUCTURE UPLOADED

=> d 11 L1 HAS NO ANSWERS L1 STR

G1 C, N

G2 Ak, NH2, NO2

G3 O

G4

G5 C, N, Zn, H

Structure attributes must be viewed using STN Express query preparation.

=> s 11 full

FULL SEARCH INITIATED 16:01:46 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 1679 TO ITERATE

100.0% PROCESSED 1679 ITERATIONS 113 ANSWERS SEARCH TIME: 00.00.01

L2 113 SEA SSS FUL L1

=> file caplus
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COST IN U.S. DOLLARS SINCE FILE TOTAL ENTRY SESSION TULL ESTIMATED COST 178.36 178.57

FILE 'CAPLUS' ENTERED AT 16:01:51 ON 15 SEP 2008
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FILE COVERS 1907 - 15 Sep 2008 VOL 149 ISS 12 FILE LAST UPDATED: 14 Sep 2008 (20080914/ED)
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Caplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2008.

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=> s 12 full
L3 11 L2
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L3 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:353001 CAPLUS

DOCUMENT NUMBER: 148:355828

TITLE: Multi-functional small molecules as anti-proliferative

agents and their preparation

INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen; Zhai,

Haixiao

PATENT ASSIGNEE(S): Curis, Inc., USA

SOURCE: PCT Int. Appl., 494pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA'	PATENT NO.						DATE APPLICAT				ION I	. O <i>V</i>			DATE		
					A2 20080320 A9 20080724			1	WO 2	007-		20070910					
NO	W:						AU,		BA,	BB,	BG,	вн,	BR,	BW,	BY,	BZ,	CA,
		CH,	CN,	co,	CR,	CU,	CZ,	DE,	DK,	DM,	DO,	DZ,	EC,	EE,	EG,	ES,	FΙ,
		GB,	GD,	GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,
		KM,	KN,	KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LY,	MA,	MD,	ME,
		MG,	MK,	MN,	MW,	MX,	MY,	MΖ,	NA,	NG,	NΙ,	NO,	NΖ,	OM,	PG,	PH,	PL,
		PT,	RO,	RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ΤJ,	TM,	TN,
		TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	ZA,	ZM,	ZW				
	RW:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FΙ,	FR,	GB,	GR,	HU,	ΙE,
							MC,										
							GΑ,										
		GH,	GM,	KΕ,	LS,	MW,	${ m MZ}$ ,	NΑ,	SD,	SL,	SZ,	${\sf TZ}$ ,	UG,	ZM,	ZW,	ΑM,	AZ,
		BY,	KG,	KΖ,	MD,	RU,	ТJ,	TM,	ΑP,	EA,	EP,	OA					
US	US 20080221132						2008	0911	1	US 2	007-	8524	58	20070910			
PRIORIT	RIORITY APPLN. INFO.:									US 2				P 20060911			
									1	US 2	007-	8958	89P	I	2	0070.	320
OTHER S	THER SOURCE (S) .						MARDAT 148.355828										

$$C \equiv CH$$
 $C \equiv CH$ 
 $C \equiv CH$ 

AB The invention relates to the compns., methods, and applications of an approach to selective inhibition of several cellular or mol. targets with a single small mol. More specifically, the present invention relates to multi-functional small mols. of formula I wherein one functionality is capable of inhibiting histone deacetylases (HDAC) and the other functionality is capable of inhibiting a different cellular or mol. pathway involved in aberrant cell proliferation, differentiation or

survival. Compds. of formula I wherein A is a pharmacophore of an anticancer agent capable of inhibiting at least one cellular or mol. pathway involved in the aberrant cell proliferation, differentiation or survival; B is a linker; C is a zinc-binding moiety; and their geometrical isomers, enantiomers, diastereoisomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, are claimed. Example compound II was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their antiproliferative activity (some data given).

IT 1011716-90-7P

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRPH (Prophetic); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prophetic starting material; preparation of multi-functional small mols. as antiproliferative agents)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[4-[[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

ANSWER 2 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN T.3

2008:351928 CAPLUS ACCESSION NUMBER:

DOCUMENT NUMBER: 148:355814

TITLE: Preparation of (aralkylamino) (phenyl) pyrrolo [2, 3d]pyrimidine derivatives for use as protein tyrosine

kinase (PTK) inhibitors

INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen

PATENT ASSIGNEE(S): Curis, Inc., USA

SOURCE: PCT Int. Appl., 123pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PA	PATENT NO.						DATE		APP	LICAT	DATE							
WO	WO 2008033745				A2 200803			0320	WO 2007-US7796					20070910				
	W:	ΑE,	AG,	AL,	AM,	ΑT,	ΑU,	ΑZ,	BA,	ВВ	, BG,	BH,	BR,	BW,	BY,	BZ,	CA,	
		CH,	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM	, DO,	DZ,	EC,	EE,	EG,	ES,	FI,	
		GB,	GD,	GE,	GH,	GM,	GΤ,	HN,	HR,	HU	, ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	
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		ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW	, ML,	MR,	ΝE,	SN,	TD,	ΤG,	BW,	
		GH,	GM,	KΕ,	LS,	MW,	MZ,	NΑ,	SD,	SL	, SZ,	TZ,	UG,	ZM,	ZW,	ΑM,	ΑZ,	
		BY,	KG,	KΖ,	MD,	RU,	ТJ,	TM										
US	US 20080161320						2008	0703		US 2007-852440				20070910				
PRIORIT	RIORITY APPLN. INFO.:									US	2006-	8436	46P		P 2	0060	911	
										US	2007-	8958	94P		P 2	0070	320	
OTHER S	THER SOURCE(S):					MARPAT 148:355814												

GI

## \* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

- AB Fused bicyclic pyrimidine derivs. I and II [Ar = aryl, substituted arylheteroaryl or heteroaryl; Q = absent or (un)substituted alkyl; X = 0, S, NH, or alkylamino; Z = O, S, NR1; Y = N or CR2; B = linker; D = C(O)NH2, NHC(S)CH3, CHC(O)NHacyl, etc.; R1 = H or (un)substituted alkyl; R2 = H, halo, (un)substituted aliphatic, aryl or heteroaryl], and their pharmaceutically acceptable salts, are prepared and disclosed as protein tyrosine kinase (PTK) inhibitors. Thus, e.g., III was prepared by N-alkylation of 1,4-dioxa-8-azaspiro[4.5]decane with 6-(4-(chloromethyl)phenyl)-N-((R)-1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4amine (preparation given) and deprotection followed by condensation with 6-aminohexanoic acid Me ester and amidation with hydroxylamine. Select I were evaluated in EGFR assays, e.g., III demonstrated an IC50 value of  $\leq 0.1$  ( $\mu$ M).
- ΙT 1011716-90-7P
  - RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)

(preparation of (aralkylamino)(phenyl)pyrrolopyrimidine derivs. for use as protein tyrosine kinase (PTK) inhibitors)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[4-[[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

L3 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:816930 CAPLUS

DOCUMENT NUMBER: 147:211903

TITLE: Preparation of pyrimidine derivatives as histone

deacetylase inhibitors

INVENTOR(S): Marconnet-Decrane, Laurence Francoise Bernadette;

Gaurrand, Sandrine Francoise Dominique; Angibaud,

Patrick Rene

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 62pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

20070116			
CA, CH,			
GB, GD,			
KM, KN,			
MG, MK,			
PT, RO,			
TR, TT,			
HU, IE,			
BF, BJ,			
BW, GH,			
AZ, BY,			
20070116			
060119			
W 20070116			

OTHER SOURCE(S): MARPAT 147:211903

GΙ

<12/04/2007>

AB The title compds. with general formula I [wherein R1 = OH or substituted phenyl; X = N or CH; R2 = amino, alkylamino, alkoxyl, OH, etc.; R3 = (un)substituted Ph, naphthalene, or heterocycle] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC50 values of 7.0 and 5.3, resp. Formulations containing I as active ingredients were also reported.

IT 944738-91-4P 944738-94-7P 944738-97-0P

944739-00-8P 944739-08-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944738-91-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(acetylamino)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-90-3 CMF C21 H26 N6 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

<12/04/2007>

RN 944738-94-7 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-amino-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-93-6
CMF C19 H24 N6 O2

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944738-97-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(2,5-dioxo-1-pyrrolidinyl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-96-9 CMF C23 H26 N6 O4

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944739-00-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(4-fluorophenoxy)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-99-2 CMF C25 H26 F N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944739-08-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944739-07-5 CMF C27 H26 N6 O4

Double bond geometry as shown.

CM 2

<12/04/2007>

CRN 76-05-1 CMF C2 H F3 O2

IT 944739-19-9P 944739-25-7P 944739-27-9P 944739-36-0P 944739-42-8P 944739-65-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944739-19-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(acetylamino)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Double bond geometry as shown.

RN 944739-25-7 CAPLUS

CN Carbamic acid, N-[(2E)-3-phenyl-1-[[4-[5-[[[(tetrahydro-2H-pyran-2-yl)oxy]amino]carbonyl]-2-pyrimidinyl]-1-piperazinyl]methyl]-2-propen-1-yl]-, 9H-fluoren-9-ylmethyl ester (CA INDEX NAME)

Double bond geometry as shown.

RN 944739-27-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-amino-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Double bond geometry as shown.

RN 944739-36-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(2,5-dioxo-1-pyrrolidinyl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 2-A

RN 944739-42-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(4-fluorophenoxy)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Double bond geometry as shown.

RN 944739-65-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Double bond geometry as shown.

4

REFERENCE COUNT:

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:816806 CAPLUS

DOCUMENT NUMBER: 147:211902

TITLE: Preparation of pyrimidine derivatives as histone

deacetylase inhibitors

INVENTOR(S): Angibaud, Patrick Rene; Van Brandt, Sven Franciscus

Anna; Marconnet-Decrane, Laurence Francoise

Bernadette; Roux, Bruno

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 63pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA	PATENT NO.						KIND DATE			APPL	ICAT		DATE				
WO	ATENT NO.  2007082880  W: AE, AG, AL,  CN, CO, CR,  GE, GH, GM,  KP, KR, KZ,  MN, MW, MX,  RS, RU, SC,  TZ, UA, UG,  RW: AT, BE, BG,  IS, IT, LT,  CF, CG, CI,  GM, KE, LS,				A1	_	2007	0726		WO 2	 007-:	20070116					
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		GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KM,	KN,
		KP,	KR,	KZ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	LY,	MA,	MD,	MG,	MK,
		MN,	MW,	MX,	MY,	MZ,	NA,	NG,	NI,	NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,
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		TZ,	UA,	UG,	US,	UZ,	VC,	VN,	ZA,	ZM,	ZW		·		,	,	·
	RW:	ΑT,	BE,	ВG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FΙ,	FR,	GB,	GR,	HU,	ΙE,
		CF,	CG,	CI,	CM,	GA,	GN,	GO,	GW,	ML,	MR,	NE,	SN,	TD,	TG,	BW,	GH,
		•	•	•	RU,	•	•	ŕ	,	·	•	•	·	•	,	,	•
PRIORITY APPLN. INFO.:						- ,				EP 2	006-	1005	71		A 2	0060	119
OTHER SOURCE(S):																	
GI		. ,															

The title compds. with general formula I [wherein R1 = OH or substituted AB phenyl; R2 = -CH2OH, -CH2OCH3, -CH2OCH2CH3, or -CH2CH(OH)CH2OH; T = N(R3), where R3 = H, alkyl, cycloalkyl, etc.; X = N or CH; Y = O, NH, CH2, etc.; n = 0-1; p = 0-1, provided that when p = 0 then n = 0 and Y = N, and -CH(R2)-Z is attached to Y; Z = (un) substituted aryl or heteroaryl] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC50 values of 7.0 and 7.1, resp. Formulations containing I as active ingredients were also reported. ΙT 944712-03-2P 944712-05-4P 944712-07-6P 944712-09-8P 944712-10-1P 944712-12-3P 944712-14-5P 944712-16-7P 944712-18-9P RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (drug candidate; preparation of pyrimidine derivs. as histone deacetylase

inhibitors)

944712-03-2 CAPLUS RN

5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(1-CN naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-02-1 CMF C21 H23 N5 O3

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

$$\begin{array}{c} F \\ | \\ F - C - CO_2H \\ | \\ F \end{array}$$

RN 944712-05-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-2-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-04-3 CMF C19 H21 N5 O3 S

CM 2

10/513699

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-07-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-[1-(phenylsulfonyl)-1H-indol-3-yl]ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-06-5 CMF C25 H26 N6 O5 S

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-09-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-

<12/04/2007>

dihydroxypropyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 944712-10-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 944712-09-8 CMF C22 H31 N5 O4

$$\begin{array}{c|c} O & OH \\ HO-CH_2-CH \\ N & N-CH \end{array}$$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-12-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R,2S)-1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-11-2 CMF C22 H31 N5 O4

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-14-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 944712-13-4 CMF C21 H23 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-16-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(2-benzofuranyl)-2-hydroxyethyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-15-6 CMF C19 H21 N5 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-18-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-3-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

Erich Leese

CM 1

CRN 944712-17-8 CMF C19 H21 N5 O3 S

<12/04/2007>

CM 2

CRN 76-05-1 CMF C2 H F3 O2

IT 944712-19-0P 944712-20-3P 944712-23-6P

944712-27-0P 944712-30-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944712-19-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-hydroxy-1-(1-naphthalenyl)ethyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

PAGE 1-A

PAGE 2-A

RN 944712-20-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-2-yl-2-hydroxyethyl)-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 944712-23-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-hydroxy-1-[1-(phenylsulfonyl)-1H-indol-3-yl]ethyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 944712-27-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 944712-30-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R,2S)-1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Absolute stereochemistry.

10/513699

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:101446 CAPLUS

DOCUMENT NUMBER: 144:192266

TITLE: Preparation of substituted propenyl piperazine

derivatives as novel inhibitors of histone deacetylase INVENTOR(S):

Van Brandt, Sven Franciscus Anna; Van Emelen, Kristof;

Angibaud, Patrick Rene; Marconnet-Decrane, Laurence

Francoise Bernadette; Arts, Janine Janssen Pharmaceutica N.V., Belg.

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V.,

SOURCE: PCT Int. Appl., 67 pp. CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA:	PATENT NO.										ICAT		DATE				
		49		A2 20060202 A3 20060608							20050725						
		AE, CN, GE,	AG, CO, GH,	AL, CR, GM,	AM, CU, HR,	AT, CZ, HU,	AU, DE, ID, LU,	AZ, DK, IL,	DM, IN,	DZ, IS,	EC, JP,	EE, KE,	EG, KG,	ES, KM,	FI, KP,	GB, KR,	GD, KZ,
		NG, SL, ZA,	NI, SM, ZM,	NO, SY, ZW	NZ, TJ,	OM, TM,	PG, TN,	PH, TR,	PL, TT,	PT, TZ,	RO, UA,	RU, UG,	SC, US,	SD, UZ,	SE, VC,	SG, VN,	SK, YU,
	RW:	IS, CF, GM,	IT, CG, KE,	LT, CI, LS,	LU, CM,	LV, GA, MZ,	CZ, MC, GN, NA,	NL, GQ,	PL, GW,	PT, ML,	RO, MR,	SE, NE,	SI, SN,	SK, TD,	TR, TG,	BF, BW,	BJ, GH,
CA	2572	11	·	A1 A1	·	2006 2006	0202	AU 2005-266311 CA 2005-2572971 EP 2005-777776						20050725			
	R:	AT, IS,	BE,	BG, LI,	CH, LT,	CY,	CZ, LV,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	IE,
JP BR KR US IN MX NO	CN 1993356  JP 2008508234  BR 2005013891  KR 2007043978  US 20070135424  IN 2007DN00658  MX 200701119  NO 2007001117  RIORITY APPLN. INFO.:						2007 2008 2008 2007 2007 2007 2007 2007	0321 0520 0426 0614 0803 0315	CN 2005-80025487 JP 2007-523072 BR 2005-13891 KR 2007-701641 US 2007-626215 IN 2007-DN658 MX 2007-1119 NO 2007-1117 EP 2004-77171						20050725 20050725 20070123 20070123 20070124 20070126 20070227 A 20040728		
OTHER SO	HER SOURCE(S):						T 14	4:192		US 2004-592357P WO 2005-EP53611 2266; MARPAT 144:192266					P 20040729		

CASALACI 144:192200; MARFAI 144:192200

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$$\begin{array}{c|c} & & & & & & & & & & & & & & & & \\ & & & & & & & & & & & & & & \\ & & & & & & & & & & & & \\ & & & & & & & & & & & \\ & & & & & & & & & & \\ & & & & & & & & & \\ & & & & & & & & & \\ & & & & & & & & \\ & & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & \\ &$$

Substituted propenyl piperazine derivs. I, wherein X is independently N or AB CH; R1 is Ph, naphthalenyl or heterocyclyl; wherein each of said Ph or naphthalenyl is optionally substituted with one or two substituents each independently selected from halo, alkyl, alkyloxy, poly-halo-alkyl, aryl, hydroxy, cyano, amino, alkylcarbonylamino, alkylsulfonylamino, hydroxycarbonyl, alkyloxycarbonyl, hydroxyalkyl, alkyloxymethyl, aminomethyl, alkylaminomethyl, alkylcarbonylaminomethyl, alkylsulfonylaminomethyl, aminosulfonyl, alkylaminosulfonyl or heterocyclyl; R2 is hydrogen, -CH2R5, trifluoromethyl, -C(0)-R6, or -CH-NR7R8; wherein each R5 is independently hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylcarbonyloxy, piperazinyl, N-methylpiperazinyl, morpholinyl, thiomorpholinyl, imidazolyl or triazolyl; each R6 is independently hydroxy, alkyloxy, amino or mono- or di(alkyl)amino, cycloalkylamino, hydroxyalkylamino, piperazinyl, N-methylpiperazinyl, morpholinyl or thiomorpholinyl; each R7 and R8 are independently hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, or mono- or di(alkyl)aminosulfonyl; R3 is hydrogen, hydroxymethyl, aminomethyl or mono- or di(alkyl)aminomethyl; R4 is hydrogen or alkyl; were prepared and having histone deacetylase inhibiting enzymic activity and to inhibit proliferative conditions, such as cancer and psoriasis. Thus, propenyl piperazine derivative II was prepared and tested in vitro and in nude mice as inhibitor of histone deacetylase and was better than R306465 after oral administration. P21 enzyme linked immunosorbent assay has been applied to determine the p21 protein expression level in human A2780 ovarian carcinoma cells. In vitro assay for inhibition of histone deacetylase is reported. P21 induction was measured as the consequence of DNA damage or as the consequence of histone deacetylase inhibition. Antiproliferative activity of title compds. was determined on A2780 cells (neg. log value of the IC50, pIC50 = 7.9-8.2).

TT 875138-85-5P 875138-87-7P 875138-88-8P 875138-89-9P 875138-90-2P 875138-91-3P 875138-93-5P 875138-94-6P 875138-98-0P 875139-00-7P 875139-02-9P 875139-04-1P 875139-06-3P 875139-07-4P 875139-09-6P 875139-11-0P 875139-13-2P 875139-14-3P 875139-15-4P 875139-17-6P 875139-19-8P 875139-20-1P 875139-21-2P 875139-23-4P 875139-24-5P 875139-25-6P 875139-26-7P 875139-27-8P 875139-30-3P 875139-31-4P 875139-69-8P

875139-70-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of substituted propenyl piperazine derivs. as novel inhibitors of histone deacetylase)

RN 875138-85-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875138-87-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-chlorophenyl)-1-(4-morpholinylmethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-86-6 CMF C23 H29 C1 N6 O3

$$\begin{array}{c|c} C1 & & & \\ & & \\ & & \\ CH = CH - CH - N & N & N \\ & & \\ & & \\ C-NH-OH \\ & \\ & \\ O \end{array}$$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875138-88-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.

RN 875138-89-9 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-88-8 CMF C19 H23 N5 O2

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

10/513699

RN 875138-90-2 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875138-91-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(acetyloxy)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875138-93-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(dimethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-92-4 CMF C22 H27 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875138-94-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(methoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875138-98-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methoxyphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-97-9 CMF C20 H25 N5 O4

Double bond geometry as shown.

CM 2

CRN 76-05-1

CMF C2 H F3 O2

RN 875139-00-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(2E)-3-(4-chlorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-99-1 CMF C19 H22 C1 N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-02-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-[1,1'-biphenyl]-4-yl-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-01-8 CMF C25 H27 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

$${\tiny \begin{array}{c}F\\F-C-CO_2H\\|\\F\end{array}}$$

RN 875139-04-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-03-0 CMF C20 H22 F3 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-06-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methylphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-05-2 CMF C20 H25 N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-07-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-methyl-1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-09-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(ethylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-08-5 CMF C23 H29 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-11-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(cyclopropylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-10-9 CMF C22 H26 N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-13-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[(methylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-12-1 CMF C20 H24 N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-14-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-15-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[[[2-(dimethylamino)ethyl]amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-17-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[[(2-hydroxyethyl)amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-16-5 CMF C21 H26 N6 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-19-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(butylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-18-7 CMF C25 H33 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-20-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-21-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-[(4-methyl-1-piperazinyl)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.

RN 875139-23-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(1H-imidazol-1-ylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-22-3 CMF C22 H25 N7 O2

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-24-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(ethoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-25-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1S)-1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

RN 875139-26-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1R)-1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry. Double bond geometry unknown.

RN 875139-27-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1S)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry. Double bond geometry unknown.

RN 875139-28-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(3-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-29-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(2-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-30-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(methoxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-31-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1S)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-

propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

● HCl

RN 875139-69-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

RN 875139-70-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

● HCl

IT 875138-54-8P 875138-59-3P 875138-62-8P

875138-66-2P 875138-70-8P 875138-73-1P

875138-77-5P 875138-78-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of substituted propenyl piperazine derivs. as novel inhibitors of histone deacetylase)

RN 875138-54-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 875138-59-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-chlorophenyl)-1-(4-morpholinylmethyl)-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 875138-62-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-methyl-3-phenyl-2-propen-1-yl)-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 875138-66-2 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(2E)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

Double bond geometry as shown.

RN 875138-70-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(dimethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 875138-73-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(methoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 875138-77-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-acetyl-2-[4-[1-[(acetyloxy)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

RN 875138-78-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-acetyl-2-[4-[1-[(acetyloxy)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]-, ethanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-77-5 CMF C28 H35 N5 O6

CM 2

CRN 144-62-7

CMF C2 H2 O4

L3 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:300395 CAPLUS

DOCUMENT NUMBER: 142:355054

TITLE: Preparation of amide derivatives as inhibitors of

histone deacetylase

INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;

Frechette, Sylvie; Vaisburg, Arkadii; Besterman,

Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.

PATENT ASSIGNEE(S): Methylgene, Inc., Can. SOURCE: PCT Int. Appl., 559 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.						KIND DATE					ICAT	ION 1	DATE							
	2005 2005									wo 2	004-	US31	20040924							
							AU,			BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,			
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FΙ,	GB,	GD,			
		GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	KP,	KR,	KΖ,	LC,			
		LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MΖ,	NA,	ΝI,			
		NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,			
		ТJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW			
	RW:	BW,	GH,	GM,	KΕ,	LS,	MW,	ΜZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,			
		ΑZ,	BY,	KG,	KΖ,	MD,	RU,	ΤJ,	TM,	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,			
		EE,	ES,	FI,	FR,	GB,	GR,	HU,	ΙE,	ΙT,	LU,	MC,	NL,	PL,	PT,	RO,	SE,			
		SI,	SK,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	ΝE,			
		SN,	TD,	ΤG																
AU 2004276337				A1		2005	0407		AU 2	004-	2763.		2	0040	924					
_	2539									-										
EP	1663	953			A1		2006	0607		EP 2	004-	7890		20040924						
	R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	ΙΤ,	LI,	LU,	NL,	SE,	MC,	PT,			
		•					RO,											HR		
	1882				Α		2006	1220	1	CN 2	004-	8003	20040924							
	2007																			
	2008																			
	2008				Α		2008	0424				-			2					
ORIT								5058	-		P 2									
												P 20031229								
															P 2					
									JP 2006-528279											
								US31			W 2	0040	924							
HER SO	HER SOURCE(S):					REAC	T 14	2 <b>:</b> 35.	5054	; MA	RPAT	142	:355	054						

GΙ

AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction The inhibitory

Ι

capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium] bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC 50 values in the range of below 1 up to 20  $\mu\text{M}$ . I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

IT 603985-86-0P 603985-88-2P 603985-90-6P 603985-94-0P 603991-95-3P 603991-96-4P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P 604784-81-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amide derivs. as inhibitors of histone deacetylase)  ${\tt RN} - 603985 - 86 - 0 - {\tt CAPLUS}$ 

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

$$^{\text{HO-CH}_2}$$
  $^{\text{O}}$   $^{\text{CH}_2}$   $^{\text{N}}$   $^{\text{N}}$   $^{\text{C}}$   $^{\text{N}}$   $^{\text{C}}$   $^{\text{N}}$   $^{\text{C}}$ 

RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]- (CA INDEX NAME)

$$CH_2-CH_2$$
 $N$ 
 $N$ 
 $N$ 
 $C-NH-OH$ 
 $O$ 

RN 603985-94-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} S & CH_2-C-N & N & N \\ \hline \\ C-NH-OH \\ O & O \end{array}$$

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[[(2-naphthalenylsulfonyl)amino]me thyl]-4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c}
O \\
S - NH - CH_2 \\
O \\
Ph - CH_2
\end{array}$$

$$\begin{array}{c|c}
N \\
N \\
N \\
O
\end{array}$$

$$\begin{array}{c}
C - NH - OH \\
O
\end{array}$$

REFERENCE COUNT:

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:300394 CAPLUS

DOCUMENT NUMBER: 142:373563

TITLE: Preparation of amide derivatives as inhibitors of

histone deacetylase

INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;

Frechette, Sylvie; Vaisburg, Arkadii; Besterman,

Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.

PATENT ASSIGNEE(S): Methylgene, Inc., Can. SOURCE: PCT Int. Appl., 389 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT	PATENT NO.								APPL	DATE										
WO 2005	0307	04		 A1		2005	0407	;	——— WO 2	004-	 US31	 590		2	0040	CH, GD, LC, NI, SY, ZW AM, DK,				
W:	ΑE,	AG,	AL,	AM,	ΑT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,				
	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FΙ,	GB,	GD,				
	GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KP,	KR,	KΖ,	LC,				
	LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MΖ,	NA,	NΙ,				
	NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,				
	ТJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW				
RW:	BW,	GH,	GM,	KΕ,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	ΑM,				
	AZ,	BY,	KG,	KZ,	MD,	RU,	ΤJ,	TM,	AT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,				
	EE,	ES,	FI,	FR,	GB,	GR,	HU,	IE,	IT,	LU,	MC,	NL,	PL,	PT,	RO,	SE,				
		•	•	•		•	•	•	•	•		•		•	,	•				
	SN,	TD,	TG	•	·	,	·	·	•	•	,	~-	•	ŕ	•	·				
JP 2008	0948	47		А		2008	0424		JP 2	007-	2813	56		2	20040924 Z, CA, CH, I, GB, GD, R, KZ, LC, Z, NA, NI, K, SL, SY, A, ZM, ZW M, ZW, AM, Z, DE, DK, I, RO, SE, L, MR, NE, 20071030 20030924 20031229 20040409					
PRIORITY APP															0030	924				
									US 2	003-	5329	73P		P 2	0031	229				
					US 2004-561082P															
OTHER SOURCE	(S):			CAS	REAC	T 14	2:37							110 2	0010	<i>J</i>				

AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction The inhibitory

Ι

capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium] bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC 50 values in the range of below 1 up to 20  $\mu\text{M}$ . I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

IT 603985-86-0P 603985-88-2P 603985-90-6P 603985-94-0P 603991-95-3P 603991-96-4P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P 604784-81-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amide derivs. as inhibitors of histone deacetylase)  ${\tt RN} - 603985 - 86 - 0 - {\tt CAPLUS}$ 

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

$$^{\text{HO-CH}_2}$$
  $^{\text{O}}$   $^{\text{CH}_2}$   $^{\text{N}}$   $^{\text{N}}$   $^{\text{C}}$   $^{\text{N}}$   $^{\text{C}}$   $^{\text{N}}$   $^{\text{C}}$ 

RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]- (CA INDEX NAME)

$$CH_2-CH_2$$
 $N$ 
 $N$ 
 $N$ 
 $C-NH-OH$ 
 $O$ 

RN 603985-94-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} S & CH_2-C-N & N & N \\ \hline \\ C-NH-OH \\ O & O \end{array}$$

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[[(2-naphthalenylsulfonyl)amino]me thyl]-4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c}
O \\
S - NH - CH_2 \\
O \\
Ph - CH_2
\end{array}$$

$$\begin{array}{c|c}
N \\
N \\
N \\
O
\end{array}$$

$$\begin{array}{c}
C - NH - OH \\
O
\end{array}$$

REFERENCE COUNT:

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737757 CAPLUS

DOCUMENT NUMBER: 139:276911

TITLE: Preparation of N-(piperazinylmethyl-,

piperidinylmethyl- and morpholinylmethyl) sulfonamides and amides as novel inhibitors of histone deacetylase

INVENTOR(S): Van Emelen, Kristof

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 69 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

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PAT	TENT	NO.			KIN	D	DATE			API	PLIC	CAT	ION I	NO.		D.	A, CH, CN, D, GE, GH, C, LK, LR, Z, OM, PH, R, TT, TZ, M, AZ, BY, K, EE, ES, I, SK, TR, N, TD, TG 20030311				
															20030311						
	W:																				
							VN,						10,	,	,	,	,	,			
	RW:												UG,	ZM,	ZW.	AM,	AZ,	BY,			
		BF,	ВJ,	CF,	CG,	CI,	CM,	GA,	GN,	, GÇ	2, (	GW,	ML,	MR,	NE,	SN,	TD,	TG			
CA	2475	766			A1		2003	0918		CA	200	03-2	2475	766		2	0030	311			
AU	2003	2187.	35		A1		2003	0922		ΑU	200	03-2	2187	35		2	0030	311			
	1485						2004			EΡ	200	03-	7119	79		2	0030	311			
EP	1485																				
	R:						ES,											PT,			
							RO,														
BR	2003	0076	06		A		2004		BR	200	03-	/606		2	0030	311					
CN	1642	948	<i>c c</i>		A 20041221 A 20050720 T 20050908					CN	200	03-8	30597	20030311 20030311 20030311							
JP	5348	5∠6 /' 33	66		T 20050908 A 20060728					JP	200	03-:	0 / 46; 5 2 4 0 '	20030311							
	1010	070N	2		A.									20030311 20030311							
	3986	0 / 0 0 . 1 5	J		T		2007							20030311							
	2836				В		2007			TW 2003-711979											
	2004				_			-						36							
	2005		016		A 1		2005	0728						84							
	2004		795		A		2004 2004	1126		MY	200	∩ 4 <b>–</b> ī	D A A 7 €	95		2	0040	910			
NO	2004	0041	35		Α		2004	0929		NO	200	04-4	4135			2	0040	929			
RIORIT	IORITY APPLN. INFO.:									US	200	02-3	3637	99P		P 2	0020	313			
										WO	200	02-I	EP14	833		A 2	0021	223			
														21							
										WO	200	03-I	EP25	10	•	W 2	0030	311			
THER SO	HER SOURCE(S):						139:	27691	11												

$$\begin{array}{c|c}
R^{2} & CH_{2} \\
\downarrow & L - A \\
\downarrow & Z
\end{array}$$

The title compds. [I; t = 0-4; Q, X, Y = N, C; Z = NH, O, CH2; R1 = CONR3R4, NHCOR7, CO(alkanediyl)SR7, etc. (wherein R3, R4 = H, OH, alkyl, etc.; R7 = H, alkyl, alkylcarbonyl, etc.); R2 = H, OH, NH2, etc.; L = NR9CO, NR9SO2, NR9CH2 (R9 = H, alkyl, cycloalkyl, etc.); A = (un)substituted Ph, cycloalkyl, pyridyl, etc.], having histone deacetylase inhibiting enzymic activity, were prepared and formulated. E.g., a multi-step synthesis of (+)-II which showed pIC50 of 7.723 against HDAC, was given.

IT 604784-81-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of N-(piperazinylmethyl-, piperidinylmethyl- and morpholinylmethyl) sulfonamides and amides as novel inhibitors of histone deacetylase)

RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[[(2-naphthalenylsulfonyl)amino]me thyl]-4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} O \\ S - NH - CH_2 \\ O \\ Ph - CH_2 \\ \end{array}$$

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737723 CAPLUS

DOCUMENT NUMBER: 139:261309

TITLE: Preparation of N-hydroxy-5-piperazino(piperidino or

diazepino)-2-pyrimidinecarboxamides and N-hydroxy-4-piperazino(piperidino or

diazepino) benzamides as new inhibitors of histone

deacetylase

INVENTOR(S): Angibaud, Patrick Rene; Pilatte, Isabelle Noeelle

Constance; Van Brandt, Sven Franciscus Anna; Roux, Bruno; Ten Holte, Peter; Verdonck, Marc Gustaaf

Celine; Meerpoel, Lieven; Dyatkin, Alexey Borisovich

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 72 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

	PAT	CENT 1	NO.			KIN	D	DATE			APE	PLI	CAT	ION 1	NO.		Ι	DATE				
	WO	2003	 0764	 00		A1	_	2003	0918		WO	20	03-1	EP25	 14		20030311					
		W:	ΑE,	AG,	AL,	AM,		AU,								BZ,	CA,	CH,	CN,			
			co,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	ΕC	j,	EE,	ES,	FI,	GB,	GD,	GE,	GH,			
								IN,														
								MD,														
								SD,														
			UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZN	1,	ZW	·	·	·		·				
		RW:	GH,	GM,	KE,	LS,	MW,	MZ,	SD,	SL,	SZ	Ζ,	TZ,	UG,	ZM,	ZW,	AM,	AZ,	BY,			
								TM,														
								IE,														
			BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GÇ	2,	GW,	ML,	MR,	ΝE,	SN,	TD,	TG			
	CA	2475	764			A1		2003	0918					2475			2	20030	311			
	ΑU	2003	2187.	36		A1		2003	AU 2003-218736							2	20030311					
	ΕP	1485	A1		2004	1215					7119	80		2	20030311							
		R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GF	۲,	ΙΤ,	LI,	LU,	NL,	SE,	MC,	PT,			
			IE,	SI,	LT,	LV,	FΙ,	RO,	MK,	CY,	ΑI	J,	TR,	BG,	CZ,	EE,	HU,	SK				
		2003		81		А		2004				_		8081					_			
	_	1639	_			А		2005	-		-			8056	-				_			
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		5348				А		2005		NZ 2003-534834												
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		1010				Α		2007		CN 2007-10005212							20030311					
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WO 2003-EP2514 W 20030311

OTHER SOURCE(S): MARPAT 139:261309

GI

The title compds. [I; n = 0-3; t = 0-4; Q, X, Y = N, C; Z = N, CH; R1 = AΒ CONR7R8, NHCOR9, CO(alkanediyl)SR9, etc. (wherein R7, R8 = H, OH, alkyl, etc.; R9 = H, alkyl, alkylcarbonyl, etc.); R2 = H, halo, OH, etc.; L = a bond, alkanediyl, alkanediyloxy, NH, CO, NHCO; each R3 = H and one H atom can be replaced by aryl; R4 = H, OH, NH2, etc.; A = (un)substituted Ph, cyclohexyl, pyridyl, etc.], having histone deacetylase inhibiting enzymic activity, were prepared and formulated. E.g., a multi-step synthesis of II which showed pIC50 of 5.121 against HDAC, was given.

ΙI

ΙT 603985-87-1P 603985-89-3P 603985-91-7P

603985-95-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of piperazino(piperidino or diazepino) substituted 2-pyrimidinecarbohydroxamic acids and N-hydroxybenzamides as new inhibitors of histone deacetylase)

RN 603985-87-1 CAPLUS

5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-CN furanyl]methyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-86-0 C21 H23 N5 O4 CMF

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-89-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-88-2 CMF C20 H21 N5 O2

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-91-7 CAPLUS

<12/04/2007>

Erich Leese

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-90-6 CMF C21 H23 N5 O2

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-95-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:2) (CA INDEX NAME)

CM 1

CRN 603985-94-0 CMF C25 H30 N6 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2 10/513699

IT 603986-73-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of piperazino(piperidino or diazepino) substituted 2-pyrimidinecarbohydroxamic acids and N-hydroxybenzamides as new inhibitors of histone deacetylase)

RN 603986-73-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(phenylmethyl)-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

3

REFERENCE COUNT:

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737586 CAPLUS

DOCUMENT NUMBER: 139:261308

TITLE: Preparation of anyl and heteroaryl hydroxamic acids as

inhibitors of histone deacetylase for treating

proliferative diseases

INVENTOR(S): Van Emelen, Kristof; Verdonck, Marc Gustaaf Celine;

Van Brandt, Sven Franciscus Anna; Angibaud, Patrick Rene; Meerpoel, Lieven; Dyatkin, Alexey Borisovich

Erich Leese

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 52 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

PA	TENT	NO.			KINI		DATE			APPL	ICAT		DATE				
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ZA	2004	0072	33		А		2005	1006			004-					0040	
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OTHER SOURCE(S): MARPAT 139:261308

<12/04/2007>

GΙ

$$R^{1}$$
  $Q=X$   $N$   $Z-R^{3}$   $R^{4}$ 

AΒ This invention comprises aryl and heteroaryl hydroxamic acids (shown as I; variables defined below; e.g. II) having histone deacetylase inhibiting enzymic activity; their preparation, compns. containing them and their use as a medicine. Compds. I show excellent in-vitro histone deacetylase inhibiting enzymic activity, have advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity), and show good metabolic stability and high bioavailability and more particular show oral bioavailability. They can also be used for detection and identification of histone deacetylase. General synthetic procedures and characterization data for twenty-seven I are included; also, prepns. of 12 intermediates are included. For example, a 59 % yield of 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5-carbohydroxamic acid was obtained by removing the O-tetrahydropyranyl group of its ester using trifluoroacetic acid; the ester was prepared in 61 % yield from N'-(ethylcarbonimidoyl)-N,N-dimethyl-1,3-propanediamine monohydrochloride, sodium 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5carboxylate, O-(tetrahydro-2H-pyran-2-yl)hydroxylamine, and 1-hydroxy-1H-benzotriazole in CH2Cl2/THF. The sodium salt was obtained by base hydrolysis of the Et ester; the ester was prepared in 73 % yield from Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate and dimethylsulfamoyl chloride; Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate was obtained in <96 % yield from Et 2-(4-benzylpiperazin-1-yl)pyrimidine-5-carboxylate by hydrogenation using Pd/C; the benzyl derivative was obtained from 1-(phenylmethyl)piperazine, (135 mL) was added gradually to a solution of potassium carbonate (0.18 mol) and 2-(methylsulfonyl)-5pyrimidinecarboxylic acid Et ester, K2CO3 in MeCN. For I: n is 0-3; Q, X and Y are N or C; Z is N or CH; R1 is -C(0)NR5R6, -N(H)C(0)R7, -C(0)-C1-6alkanediylSR7, -NR8C(0)N(OH)R7, -NR8C(0)C1-6alkanediylSR7, -NR8C(O)C:N(OH)R7 or another Zn-chelating-group; R2 is H, halo, hydroxy, amino, nitro, C1-6alkyl, C1-6alkyloxy, trifluoromethyl, di(C1-6-alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl. R3 is H, C1-6-alkyl, arylC2-6alkenediyl, furanylcarbonyl, naphthalenylcarbonyl, -C(0)phenylR9, C1-6alkylaminocarbonyl, aminosulfonyl, arylaminosulfonyl, aminosulfonylamino, di (C1-6-alkyl) aminosulfonylamino, arylaminosulfonylamino, aminosulfonylaminoC1-6-alkyl, di(C1-6alkyl)aminosulfonylaminoC1-6-alkyl, arylaminosulfonylaminoC1-6alkyl, di(C1-6-alkyl)aminoC1-6alkyl, C11-12-alkylsulfonyl, di(C1-6alkyl)aminosulfonyl, trihaloC1-6-alkylsulfonyl, di(aryl)C1-6alkylcarbonyl, thiophenylC1-6alkylcarbonyl, pyridinylcarbonyl or arylC1-6alkylcarbonyl. R4 is H, hydroxy, amino, hydroxyC1-6alkyl, C1-6alkyl, C1-6alkyloxy,

arylC1-6alkyl, aminocarbonyl, hydroxycarbonyl, aminoC1-6-alkyl, aminocarbonylC1-6-alkyl, hydroxycarbonylC1-6-alkyl, hydroxyaminocarbonyl, C1-6-alkyloxycarbonyl, C1-6-alkylaminoC1-6-alkyl or di(C1-6-alkyl)aminoC1-6-alkyl; when R3 and R4 are present on the same C atom, R3 and R4 together may form -C(0)-NH-CH2-NR10- wherein R10 is H or aryl; when R3 and R4 are present on adjacent C atoms, R3 and R4 together may form :CH-CH:CH-CH:; addnl. details are given in the claims.

IT 603991-96-4P

RL: ARG (Analytical reagent use); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

IT 603991-95-3P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P

RL: ARG (Analytical reagent use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} S & CH_2-C-N & N & N \\ \hline \\ C-NH-OH \\ \hline \\ O & \\ \end{array}$$

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

IT 603992-32-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

RN 603992-32-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]- (CA INDEX NAME)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

## 10/513699

ANSWER 11 OF 11 CAPLUS COPYRIGHT 2008 ACS on STN T.3

1986:442843 CAPLUS ACCESSION NUMBER:

105:42843 DOCUMENT NUMBER: ORIGINAL REFERENCE NO.: 105:7101a,7104a

TITLE: Pyrimidinylpiperazines

Kihara, Noriaki; Ishida, Tatsukazu; Isayama, Shigeru; INVENTOR(S): Ishitoku, Takeshi; Tan, Hiroaki; Takahashi, Katsuya

PATENT ASSIGNEE(S): Mitsui Petrochemical Industries, Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 28 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 61043173	A	19860301	JP 1984-163771	19840806
JP 05022702	В	19930330		
PRIORITY APPLN. INFO.:			JP 1984-163771	19840806
GI				

$$\mathbb{R}^{3}$$
 COX  $\mathbb{R}^{1}\mathbb{N}$   $\mathbb{R}^{2}$   $\mathbb{R}^{2}\mathbb{N}$   $\mathbb{R}^{2}$   $\mathbb{R}^{2}\mathbb{N}$   $\mathbb{N}$   $\mathbb{R}^{2}\mathbb{N}$   $\mathbb{N}$   $\mathbb$ 

- AB The title compds. [I, R1 = H, substituted Me, alkoxycarbonyl; R2, R3 = H, substituted alkyl; X = alkoxy, OH, (substituted) NH2; n = 2, 3], useful as herbicides against common weeds (no data), were prepared Thus, the piperazinecarboxamidine derivative II sulfate reacted with MeOCH:C(COMe)CO2Me in MeOH/aqueous NaOH at room temperature overnight to give 88% I (R1 = PhCH2,
- R2 = H, R3 = Me, X = OMe).
- ΙT 102976-25-0P 102976-32-9P

RL: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of, as herbicide)

102976-25-0 CAPLUS RN

5-Pyrimidinecarboxamide, 4-methyl-N-(phenylmethoxy)-2-[4-(phenylmethyl)-1-CN piperazinyl]- (CA INDEX NAME)

$$Ph-CH_2-O-NH-C$$
 $N$ 
 $N$ 
 $N$ 
 $N$ 
 $CH_2-Ph$ 
 $CH_2-Ph$ 

<12/04/2007>

RN 102976-32-9 CAPLUS

CN 5-Pyrimidinecarboxamide, N-methoxy-4-methyl-2-[4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

=> file reg
COST IN U.S. DOLLARS

FULL ESTIMATED COST

SINCE FILE TOTAL
ENTRY SESSION
60.43 239.00

SINCE FILE TOTAL ENTRY SESSION

CA SUBSCRIBER PRICE

-8.80 -8.80

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STRUCTURE FILE UPDATES: 14 SEP 2008 HIGHEST RN 1049627-95-3 DICTIONARY FILE UPDATES: 14 SEP 2008 HIGHEST RN 1049627-95-3

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http://www.cas.org/support/stngen/stndoc/properties.html

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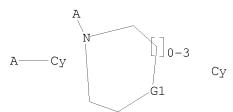
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ring nodes :
5 6 7 8 9 10
chain bonds :
1-4 5-11
ring bonds :
5-6 5-7 6-8 7-9 8-10 9-10
exact/norm bonds :
1-4 5-6 5-7 5-11 6-8 7-9 8-10 9-10
G1:C, N
Match level :
1:Atom 2:Atom 4:CLASS 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:CLASS
Generic attributes :
1:
                     : Unsaturated
Saturation
Number of Carbon Atoms : less than 7
Type of Ring System : Monocyclic
Element Count :
Node 1: Limited
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   N, N0-3
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## 10/513699

## L4 STRUCTURE UPLOADED

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G1 C, N

Structure attributes must be viewed using STN Express query preparation.

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ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 20 21 22 23 24 25 26 27 28 29 30
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chain bonds :

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ring bonds :
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exact/norm bonds :
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  50-52 52-53 53-54 54-55 56-57 56-58 60-61
exact bonds :
54 - 56
isolated ring systems :
containing 1 : 7 : 20 : 26 : 39 : 49 :
G1:C,N
G2:Ak, NH2, NO2
G3:0
G4: [*1], [*2], [*3], [*4], [*5]
Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 19:CLASS 20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom
26:Atom 27:Atom 28:Atom 29:Atom 30:Atom 31:Atom 32:CLASS 34:CLASS 39:Atom 40:Atom 41:Atom 42:Atom 43:Atom 44:Atom 45:CLASS 46:CLASS 47:CLASS 49:Atom
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  61:Atom
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100.0% PROCESSED 596714 ITERATIONS
                                                                                                                                                                              10223 ANSWERS
SEARCH TIME: 00.00.08
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COST IN U.S. DOLLARS
                                                                                                                                            SINCE FILE TOTAL
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FULL ESTIMATED COST ENTRY SESSION 179.28 418.28

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE TOTAL
ENTRY SESSION

CA SUBSCRIBER PRICE

0.00 -8.80

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FILE COVERS 1907 - 15 Sep 2008 VOL 149 ISS 12 FILE LAST UPDATED: 14 Sep 2008 (20080914/ED)

Caplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2008.

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=> s 16 full L7 4042 L6

=> s 17 and py<2003 22958911 PY<2003

L8 2880 L7 AND PY<2003

=> file reg

COST IN U.S. DOLLARS

SINCE FILE TOTAL
ENTRY SESSION
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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE TOTAL

CA SUBSCRIBER PRICE

ENTRY SESSION

-8.80

FILE 'REGISTRY' ENTERED AT 16:06:14 ON 15 SEP 2008
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STRUCTURE FILE UPDATES: 14 SEP 2008 HIGHEST RN 1049627-95-3 DICTIONARY FILE UPDATES: 14 SEP 2008 HIGHEST RN 1049627-95-3

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TSCA INFORMATION NOW CURRENT THROUGH July 5, 2008.

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http://www.cas.org/support/stngen/stndoc/properties.html

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ring nodes :
1 2 3 4 5
              6 19 20 21 22 23
chain bonds :
2-23 5-13 13-14 20-25 25-26 25-27 27-28 27-29 28-30
ring bonds :
1-2 \quad 1-6 \quad 2-3 \quad 3-4 \quad 4-5 \quad 5-6 \quad 19-20 \quad 19-24 \quad 20-21 \quad 21-22 \quad 22-23 \quad 23-24
exact/norm bonds :
1-2 1-6 2-3 2-23 3-4 4-5 5-6 5-13 13-14 25-26 25-27 27-28
exact bonds :
20-25 27-29 28-30
normalized bonds :
19-20 19-24 20-21 21-22 22-23 23-24
isolated ring systems :
containing 1 :
```

G1:C, N

G2:Ak, NH2, NO2

G3:0

G4

G5:C,N,Zn,H

Match level:

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 13:CLASS 14:Atom 19:Atom 20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS 30:CLASS

L9 STRUCTURE UPLOADED

=> d 19

L9 HAS NO ANSWERS

L9 STR

G1 C, N

G2 Ak, NH2, NO2

G3 O

G4

G5 C, N, Zn, H

Structure attributes must be viewed using STN Express query preparation.

=> s 19 full

FULL SEARCH INITIATED 16:07:27 FILE 'REGISTRY' FULL SCREEN SEARCH COMPLETED - 433 TO ITERATE

100.0% PROCESSED 433 ITERATIONS 112 ANSWERS

SEARCH TIME: 00.00.01

L10 112 SEA SSS FUL L9

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE TOTAL
ENTRY SESSION
178.82 600.66

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

CA SUBSCRIBER PRICE

SINCE FILE TOTAL
ENTRY SESSION
-8.80

FILE 'CAPLUS' ENTERED AT 16:07:34 ON 15 SEP 2008
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FILE COVERS 1907 - 15 Sep 2008 VOL 149 ISS 12 FILE LAST UPDATED: 14 Sep 2008 (20080914/ED)

Caplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2008.

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

Erich Leese

http://www.cas.org/legal/infopolicy.html

=> s 110 full L11 13 L10

=> d ibib abs hitstr tot

<12/04/2007>

L11 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:556979 CAPLUS

DOCUMENT NUMBER: 148:538314

TITLE: Preparation of tricyclic hydroxamic acids as

inhibitors of histone deacetylase

INVENTOR(S): Shapiro, Gideon; Moncuso, John; Pierre, Tessier; Leit,

Silvana; Deziel, Robert; David, Smil; Richard,

Chesworth; Chantigny, Yves Andre; Patrick, Beaulieu

PATENT ASSIGNEE(S): Methygene Inc., Can.; En Vivo Pharmaceuticals, Inc.

SOURCE: PCT Int. Appl., 405pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.					KIND DATE			APPLICATION NO.										
WO	2008	08055068			A2	_	2008	0508	1	wo 2	 007-1	JS82	 668	20071026				
	W:	ΑE,	AG,	AL,	AM,	ΑT,	ΑU,	ΑZ,	BA,	BB,	BG,	BH,	BR,	BW,	BY,	BZ,	CA,	
		CH,	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DO,	DZ,	EC,	EE,	EG,	ES,	FI,	
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		KM,	KN,	KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LY,	MA,	MD,	ME,	
		MG,	MK,	MN,	MW,	MX,	MY,	MZ,	NA,	NG,	NI,	NO,	NΖ,	OM,	PG,	PH,	PL,	
		PT,	RO,	RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ΤJ,	TM,	TN,	
		TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	ZA,	ZM,	ZW					
	RW:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	ΙE,	
		IS,	ΙΤ,	LT,	LU,	LV,	MC,	MT,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,	
		ΒJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	$\mathrm{ML}_{,}$	MR,	NE,	SN,	TD,	ΤG,	BW,	
		GH,	GM,	ΚE,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	ΑZ,	
		BY,	KG,	KΖ,	MD,	RU,	ТJ,	TM										
US	US 20080207590				A1		2008	0828	1	US 2	007-	9251	51	20071026				
PRIORIT	PRIORITY APPLN. INFO.:								US 2006-863347P					P 20061028				
							US 2007-884287P					]	P 20070110					

OTHER SOURCE(S): MARPAT 148:538314

GΙ

AB The title compds. I [Z = N(R1)OR2, H; L = a bond, N(OR2); when L = N(OR2), Z = H; when Z = H, L = N(OR2); R1, R2 = H, alkyl, aryl, etc.; J = a bond, :CH-, alkyl, alkyl(heteroalkyl)alkyl, etc.; Q = diazepine, pyrrolidine, diazabicyclo[3.3.1]nonane, etc.; B = dibenzo[b,f][1,4]oxazepine, benzo[b]pyrido[2,3-e][1,4]diazepine, benzo[f]thieno[2,3-b][1,4]oxazepine, etc.;], useful for the inhibition of histone deacetylase, were prepared E.g., a 3-step synthesis of II, starting from 10,11-

dihydrodibenz[b,f][1,4]oxazepin-11-one, was given. All exemplified compds. I have an IC50 of  $\leq$  10  $\mu\text{M}$  against one of more of HDAC-1 through HDAC-11 (data for representative compds. I were given). Pharmaceutical composition comprising the compound I and methods of treating polyglutamine (polyQ) expansion diseases such as Huntington's disease, are disclosed.

IT 1024007-45-1P 1024009-50-4P 1024009-80-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of tricyclic hydroxamic acids as inhibitors of histone deacetylase)

RN 1024007-45-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2-chlorodibenz[b,f][1,4]oxazepin-11-yl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 1024009-50-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 1024009-80-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]hexahydro-1H-1,4-diazepin-1-yl]-N-hydroxy- (CA INDEX NAME)

L11 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:353109 CAPLUS

DOCUMENT NUMBER: 148:379651

TITLE: Pyrimidine derivatives as tyrosine kinase inhibitors

containing a zinc binding moiety and their preparation

INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen; Zhai,

Haixiao

PATENT ASSIGNEE(S): Curis, Inc., USA

SOURCE: PCT Int. Appl., 81pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

P	PATENT NO.					KIND DATE				APPL	ICAT		DATE				
W(	2008 C	08033746			A2	_	2008	0320		——— WO 2	 007-1	07-US77970			20070910		
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		CH,	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DO,	DZ,	EC,	EE,	EG,	ES,	FΙ,
		GB,	GD,	GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,
		KM,	KN,	KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LY,	MA,	MD,	ME,
		MG,	MK,	MN,	MW,	MX,	MY,	MZ,	NA,	NG,	NΙ,	NO,	NZ,	OM,	PG,	PH,	PL,
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	RW:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FΙ,	FR,	GB,	GR,	HU,	IE,
		IS,	IT,	LT,	LU,	LV,	MC,	MT,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,
		ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	${ m ML}$ ,	MR,	ΝE,	SN,	TD,	ΤG,	BW,
		GH,	GM,	KΕ,	LS,	MW,	${ m MZ}$ ,	NΑ,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	ΑZ,
		BY,	KG,	KΖ,	MD,	RU,	ТJ,	$_{ m TM}$									
U	S 2008	0125	440		A1		2008	0529		US 2007-852450					2	0070	910
PRIORI:	PRIORITY APPLN. INFO.:			.:						US 2	006-	8437.	30P	]	2	0060	911
										US 2	007-	8959	01P	]	2	0070.	320
OTHER SOURCE(S):					MAR)	PAT	148:	3796.	51								

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The invention relates to tyrosine kinase inhibitors of formula I and II AB that contain a zinc-binding moiety and their use in the treatment of tyrosine related diseases and disorders such as cancer. The said derivs. may further act as HDAC inhibitors. Compds. of formula I and II wherein Cz is (un)substituted (hetero)aryl, and (un)substituted heterocyclic; Ar is (un)substituted (hetero)aryl; X3 is NH, alkylamino, O, and S; Z2 is O, S, NH and alkylamino; Y2 is N, CH, C-halo, C-(hetero)aryl, etc.; R21 is H and aliphatic; B is a liner. C is urea, thiourea, acetyl, thioacetyl, etc.; R8 is H, acyl, and (un)substituted aliphatic group; and their geometric isomers, enantiomers, diastereoisomers, racemates, pharmaceutically acceptable salts, and solvates thereof, are claimed. Example compound III was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their tyrosine kinase inhibitory activity. ΙT

1012886-07-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(drug candidate; preparation of pyrimidine derivs. as tyrosine kinase inhibitors containing a zinc binding moiety)

RN 1012886-07-5 CAPLUS

5-Pyrimidinecarboxamide, 2-[4-[6-[[5-[[(2-chloro-6-CN methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-2-methyl-4-pyrimidinyl]-1piperazinyl]-N-hydroxy- (CA INDEX NAME)

ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE

L11 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:353001 CAPLUS

DOCUMENT NUMBER: 148:355828

TITLE: Multi-functional small molecules as anti-proliferative

agents and their preparation

INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen; Zhai,

Haixiao

PATENT ASSIGNEE(S): Curis, Inc., USA

SOURCE: PCT Int. Appl., 494pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PAT	PATENT NO.					KIND DATE			APPL	ICAT	ION I	DATE						
	WO 2008033747 WO 2008033747														20070910			
we.	W:	AE, CH, GB, KM, MG,	AG, CN, GD, KN, MK,	AL, CO, GE, KP, MN,	AM, CR, GH, KR, MW,	AT, CU, GM, KZ, MX,	AU, CZ, GT, LA, MY,	AZ, DE, HN, LC, MZ,	DK, HR, LK, NA,	DM, HU, LR, NG,	DO, ID, LS, NI,	DZ, IL, LT, NO,	EC, IN, LU, NZ,	EE, IS, LY, OM,	EG, JP, MA, PG,	ES, KE, MD, PH,	FI, KG, ME, PL,	
	R₩:	TR, AT, IS, BJ, GH,	TT, BE, IT, CF, GM,	TZ, BG, LT, CG, KE,	UA, CH, LU, CI, LS,	UG, CY, LV, CM, MW,	SD, US, CZ, MC, GA, MZ, TJ,	UZ, DE, MT, GN, NA,	VC, DK, NL, GQ, SD,	VN, EE, PL, GW, SL,	ZA, ES, PT, ML, SZ,	ZM, FI, RO, MR, TZ,	ZW FR, SE, NE,	GB, SI, SN,	GR, SK, TD,	HU, TR, TG,	IE, BF, BW,	
PRIORITY	US 20080221132 RIORITY APPLN. INFO.:						2008			US 2 US 2 US 2	006-	8435	90P	_	2	00709 00609 00703	911	

$$C\equiv CH$$
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AB The invention relates to the compns., methods, and applications of an approach to selective inhibition of several cellular or mol. targets with a single small mol. More specifically, the present invention relates to multi-functional small mols. of formula I wherein one functionality is capable of inhibiting histone deacetylases (HDAC) and the other

functionality is capable of inhibiting a different cellular or mol. pathway involved in aberrant cell proliferation, differentiation or survival. Compds. of formula I wherein A is a pharmacophore of an anticancer agent capable of inhibiting at least one cellular or mol. pathway involved in the aberrant cell proliferation, differentiation or survival; B is a linker; C is a zinc-binding moiety; and their geometrical isomers, enantiomers, diastereoisomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, are claimed. Example compound II was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their antiproliferative activity (some data given).

IT 1011716-90-7P 1012886-07-5P

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRPH (Prophetic); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prophetic starting material; preparation of multi-functional small mols. as antiproliferative agents)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[4-[[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

RN 1012886-07-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[6-[[5-[[(2-chloro-6-methylphenyl)amino]carbonyl]-2-thiazolyl]amino]-2-methyl-4-pyrimidinyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

ONE OR MORE TAUTOMERIC DOUBLE BONDS NOT DISPLAYED IN THE STRUCTURE

L11 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

2008:351928 CAPLUS ACCESSION NUMBER:

DOCUMENT NUMBER: 148:355814

TITLE: Preparation of (aralkylamino) (phenyl) pyrrolo [2, 3-

d]pyrimidine derivatives for use as protein tyrosine

kinase (PTK) inhibitors

INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen

PATENT ASSIGNEE(S): Curis, Inc., USA

SOURCE: PCT Int. Appl., 123pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.					KIND DATE									DATE			
WO	WO 2008033745							 WO 2	007-	JS77:	 968	20070910					
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		CH,	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DO,	DZ,	EC,	EE,	EG,	ES,	FΙ,
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		BY,	KG,	KΖ,	MD,	RU,	ТJ,	TM									
US	2008	0161	320		A1		2008	0703		US 2	007-	8524	40		2	00709	910
PRIORIT	PRIORITY APPLN. INFO.:			.:						US 2	006-	8436	46P		P 2	00609	911
										US 2	007-	8958	94P		P 2	00703	320
OTHER SOURCE(S):					MAR	PAT	148:	3558:	14								

GI

## \* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

- AB Fused bicyclic pyrimidine derivs. I and II [Ar = aryl, substituted arylheteroaryl or heteroaryl; Q = absent or (un)substituted alkyl; X = 0, S, NH, or alkylamino; Z = O, S, NR1; Y = N or CR2; B = linker; D = C(O)NH2, NHC(S)CH3, CHC(O)NHacyl, etc.; R1 = H or (un)substituted alkyl; R2 = H, halo, (un)substituted aliphatic, aryl or heteroaryl], and their pharmaceutically acceptable salts, are prepared and disclosed as protein tyrosine kinase (PTK) inhibitors. Thus, e.g., III was prepared by N-alkylation of 1,4-dioxa-8-azaspiro[4.5]decane with 6-(4-(chloromethyl)phenyl)-N-((R)-1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4amine (preparation given) and deprotection followed by condensation with 6-aminohexanoic acid Me ester and amidation with hydroxylamine. Select I were evaluated in EGFR assays, e.g., III demonstrated an IC50 value of  $\leq 0.1$  ( $\mu$ M).
- ΙT 1011716-90-7P
  - RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)

(preparation of (aralkylamino)(phenyl)pyrrolopyrimidine derivs. for use as protein tyrosine kinase (PTK) inhibitors)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[4-[[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

L11 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:816930 CAPLUS

DOCUMENT NUMBER: 147:211903

TITLE: Preparation of pyrimidine derivatives as histone

deacetylase inhibitors

INVENTOR(S): Marconnet-Decrane, Laurence Francoise Bernadette;

Gaurrand, Sandrine Francoise Dominique; Angibaud,

Patrick Rene

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 62pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.					D	DATE		APPLICATION NO.						DATE			
2007	0828	74		A1 20070726			WO 2007-EP50371						20070116				
W:	ΑE,	AG,	AL,	ΑM,	ΑT,	ΑU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,	
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	GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	KM,	KN,	
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	RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ΤJ,	TM,	TN,	TR,	TT,	
	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	ZA,	ZM,	ZW							
RW:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	ΙE,	
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	GM,	KΕ,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	ΑM,	ΑZ,	BY,	
	KG,	KΖ,	MD,	RU,	ΤJ,	TM											
. 2630	717			A1		2007	0726	(	CA 2	007-	2630'	717		20070116			
PRIORITY APPLN. INFO.:			.:					EP 2006-100570					2	A 20060119			
								1	WO 2	007-1	EP503	371	Ī	W 2	0070	116	
	2007 W: RW:	20070828 W: AE, CN, GE, KP, MN, RS, TZ, RW: AT, IS, CF, GM, KG,	2007082874 W: AE, AG, CN, CO, GE, GH, KP, KR, MN, MW, RS, RU, TZ, UA, RW: AT, BE, IS, IT, CF, CG, GM, KE, KG, KZ, 2630717 Y APPLN. INFO	2007082874 W: AE, AG, AL, CN, CO, CR, GE, GH, GM, KP, KR, KZ, MN, MW, MX, RS, RU, SC, TZ, UA, UG, RW: AT, BE, BG, IS, IT, LT, CF, CG, CI, GM, KE, LS, KG, KZ, MD, 2630717 Y APPLN. INFO.:	2007082874 A1 W: AE, AG, AL, AM, CN, CO, CR, CU, GE, GH, GM, GT, KP, KR, KZ, LA, MN, MW, MX, MY, RS, RU, SC, SD, TZ, UA, UG, US, RW: AT, BE, BG, CH, IS, IT, LT, LU, CF, CG, CI, CM, GM, KE, LS, MW, KG, KZ, MD, RU, 2630717 A1 Y APPLN. INFO.:	2007082874 A1  W: AE, AG, AL, AM, AT, CN, CO, CR, CU, CZ, GE, GH, GM, GT, HN, KP, KR, KZ, LA, LC, MN, MW, MX, MY, MZ, RS, RU, SC, SD, SE, TZ, UA, UG, US, UZ, RW: AT, BE, BG, CH, CY, IS, IT, LT, LU, LV, CF, CG, CI, CM, GA, GM, KE, LS, MW, MZ, KG, KZ, MD, RU, TJ, 2630717 Y APPLN. INFO.:	2007082874  W: AE, AG, AL, AM, AT, AU, CN, CO, CR, CU, CZ, DE, GE, GH, GM, GT, HN, HR, KP, KR, KZ, LA, LC, LK, MN, MW, MX, MY, MZ, NA, RS, RU, SC, SD, SE, SG, TZ, UA, UG, US, UZ, VC, RW: AT, BE, BG, CH, CY, CZ, IS, IT, LT, LU, LV, MC, CF, CG, CI, CM, GA, GN, GM, KE, LS, MW, MZ, NA, KG, KZ, MD, RU, TJ, TM 2630717  Y APPLN. INFO.:	2007082874  W: AE, AG, AL, AM, AT, AU, AZ, CN, CO, CR, CU, CZ, DE, DK, GE, GH, GM, GT, HN, HR, HU, KP, KR, KZ, LA, LC, LK, LR, MN, MW, MX, MY, MZ, NA, NG, RS, RU, SC, SD, SE, SG, SK, TZ, UA, UG, US, UZ, VC, VN, RW: AT, BE, BG, CH, CY, CZ, DE, IS, IT, LT, LU, LV, MC, NL, CF, CG, CI, CM, GA, GN, GQ, GM, KE, LS, MW, MZ, NA, SD, KG, KZ, MD, RU, TJ, TM  2630717  A1 20070726	2007082874  W: AE, AG, AL, AM, AT, AU, AZ, BA, CN, CO, CR, CU, CZ, DE, DK, DM, GE, GH, GM, GT, HN, HR, HU, ID, KP, KR, KZ, LA, LC, LK, LR, LS, MN, MW, MX, MY, MZ, NA, NG, NI, RS, RU, SC, SD, SE, SG, SK, SL, TZ, UA, UG, US, UZ, VC, VN, ZA, RW: AT, BE, BG, CH, CY, CZ, DE, DK, IS, IT, LT, LU, LV, MC, NL, PL, CF, CG, CI, CM, GA, GN, GQ, GW, GM, KE, LS, MW, MZ, NA, SD, SL, KG, KZ, MD, RU, TJ, TM  2630717  A1 20070726	2007082874  W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, GE, GH, GM, GT, HN, HR, HU, ID, IL, KP, KR, KZ, LA, LC, LK, LR, LS, LT, MN, MW, MX, MY, MZ, NA, NG, NI, NO, RS, RU, SC, SD, SE, SG, SK, SL, SM, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, IS, IT, LT, LU, LV, MC, NL, PL, PT, CF, CG, CI, CM, GA, GN, GQ, GW, ML, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, KG, KZ, MD, RU, TJ, TM  2630717  A1 20070726  CA 2 WO 2	2007082874  M: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, KG, KZ, MD, RU, TJ, TM  2630717  A1 20070726  CA 2007-1	2007082874  A1 20070726 W0 2007-EP503  W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW  RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, KG, KZ, MD, RU, TJ, TM  2630717  A1 20070726 CA 2007-2630  Y APPLN. INFO.:  EP 2006-1005	2007082874  A1 20070726 WO 2007-EP50371  W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW  RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, KG, KZ, MD, RU, TJ, TM  2630717  Y APPLN. INFO::  CA 2007-2630717  EP 2006-100570  WO 2007-EP50371	2007082874  A1 20070726 WO 2007-EP50371  W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW  RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, KG, KZ, MD, RU, TJ, TM  2630717  A1 20070726 CA 2007-2630717  Y APPLN. INFO::  EP 2006-100570  WO 2007-EP50371	2007082874  A1 20070726 W0 2007-EP50371  W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW  RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, KG, KZ, MD, RU, TJ, TM  2630717  A1 20070726 CA 2007-2630717  Y APPLN. INFO::  EP 2006-100570 A 2 WO 2007-EP50371 W 2	2007082874  A1 20070726 W0 2007-EP50371 20070 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, KG, KZ, MD, RU, TJ, TM  20070 20070 20070 20070 20070 20070	

OTHER SOURCE(S): MARPAT 147:211903

GΙ

AB The title compds. with general formula I [wherein R1 = OH or substituted phenyl; X = N or CH; R2 = amino, alkylamino, alkoxyl, OH, etc.; R3 = (un)substituted Ph, naphthalene, or heterocycle] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC50 values of 7.0 and 5.3, resp. Formulations containing I as active ingredients were also reported.

IT 944738-91-4P 944738-94-7P 944738-97-0P

944739-00-8P 944739-08-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944738-91-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(acetylamino)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-90-3 CMF C21 H26 N6 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

<12/04/2007>

RN 944738-94-7 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-amino-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-93-6
CMF C19 H24 N6 O2

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944738-97-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(2,5-dioxo-1-pyrrolidinyl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-96-9 CMF C23 H26 N6 O4

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944739-00-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(4-fluorophenoxy)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-99-2 CMF C25 H26 F N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944739-08-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944739-07-5 CMF C27 H26 N6 O4

Double bond geometry as shown.

CM 2

<12/04/2007>

10/513699

CRN 76-05-1 CMF C2 H F3 O2

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:816806 CAPLUS

DOCUMENT NUMBER: 147:211902

TITLE: Preparation of pyrimidine derivatives as histone

deacetylase inhibitors

INVENTOR(S): Angibaud, Patrick Rene; Van Brandt, Sven Franciscus

Anna; Marconnet-Decrane, Laurence Francoise

Bernadette; Roux, Bruno

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 63pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.					KIND		DATE		APPLICATION NO.						DATE		
WO	2007	07082880				A1 200				 WO 2	 007-:		20070116				
	W:	ΑE,	AG,	AL,	ΑM,	ΑT,	ΑU,	ΑZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FΙ,	GB,	GD,
		GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	KM,	KN,
		KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	LY,	MA,	MD,	MG,	MK,
		MN,	MW,	MX,	MY,	MΖ,	NA,	NG,	ΝI,	NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,
		RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ТJ,	TM,	TN,	TR,	ΤΤ,
		TZ,	UA,	UG,	US,	UΖ,	VC,	VN,	ZA,	ZM,	ZW						
	RW:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	ΙE,
		IS,	IT,	LT,	LU,	LV,	MC,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,	ВJ,
		CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	ΝE,	SN,	TD,	TG,	BW,	GH,
		GM,	ΚE,	LS,	MW,	MΖ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	ΑZ,	BY,
		KG,	KΖ,	MD,	RU,	ΤJ,	$_{ m TM}$										
PRIORITY	PRIORITY APPLN. INFO.:									EP 2	006-	1005	71		A 2	0060	119
OTHER SOURCE(S): GI				MAR	PAT	147:	2119	02									

The title compds. with general formula I [wherein R1 = OH or substituted AB phenyl; R2 = -CH2OH, -CH2OCH3, -CH2OCH2CH3, or -CH2CH(OH)CH2OH; T = N(R3), where R3 = H, alkyl, cycloalkyl, etc.; X = N or CH; Y = O, NH, CH2, etc.; n = 0-1; p = 0-1, provided that when p = 0 then n = 0 and Y = N, and -CH(R2)-Z is attached to Y; Z = (un) substituted aryl or heteroaryl] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC50 values of 7.0 and 7.1, resp. Formulations containing I as active ingredients were also reported. ΙT 944712-03-2P 944712-05-4P 944712-07-6P 944712-09-8P 944712-10-1P 944712-12-3P 944712-14-5P 944712-16-7P 944712-18-9P RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (drug candidate; preparation of pyrimidine derivs. as histone deacetylase

inhibitors)

944712-03-2 CAPLUS RN

5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(1-CN naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-02-1 CMF C21 H23 N5 O3

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

$$\begin{array}{c} F \\ | \\ F - C - CO_2H \\ | \\ F \end{array}$$

RN 944712-05-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-2-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-04-3 CMF C19 H21 N5 O3 S

CM 2

10/513699

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-07-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-[1-(phenylsulfonyl)-1H-indol-3-yl]ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-06-5 CMF C25 H26 N6 O5 S

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-09-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-

<12/04/2007>

dihydroxypropyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 944712-10-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 944712-09-8 CMF C22 H31 N5 O4

$$\begin{array}{c|c} O & OH \\ HO-CH_2-CH \\ N & N-CH \end{array}$$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-12-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R,2S)-1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-11-2 CMF C22 H31 N5 O4

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-14-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 944712-13-4 CMF C21 H23 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-16-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(2-benzofuranyl)-2-hydroxyethyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-15-6 CMF C19 H21 N5 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-18-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-3-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-17-8 CMF C19 H21 N5 O3 S

<12/04/2007>

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & \\ & & \\ &$$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

REFERENCE COUNT:

3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:485854 CAPLUS

DOCUMENT NUMBER: 146:482095

TITLE: Preparation of squaric acid derivatives as histone

deacetylase (HDAC) inhibitors for the treatment of

proliferative diseases

INVENTOR(S):
Van Emelen, Kristof

PATENT ASSIGNEE(S): Janssen Pharmaceutica N. V., Belq.

SOURCE: PCT Int. Appl., 37pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

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P	ATENT	NO.			KIND DA					APPLICATION NO.					DATE					
W	O 200	2007048767				_	2007	0503		——— WO 2	006-	 EP67		20061023						
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		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,			
		GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	KM,	KN,			
		KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	LY,	MA,	MD,	MG,	MK,			
		MN,	MW,	MX,	MY,	MZ,	NA,	NG,	ΝI,	NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,			
		RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ТJ,	TM,	TN,	TR,	ΤΤ,			
		TZ,	UA,	UG,	US,	UΖ,	VC,	VN,	ZA,	ZM,	ZW									
	RW	: AT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	ΙE,			
		IS,	ΙΤ,	LT,	LU,	LV,	MC,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,	ΒJ,			
		CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	G₩,	ML,	MR,	ΝE,	SN,	TD,	ΤG,	BW,	GH,			
		GM,	KΕ,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	ΑZ,	BY,			
		KG,	KΖ,	MD,	RU,	ΤJ,	TM													
A	U 200	63079	18		A1		2007	0503		AU 2	006-	3079	20061023							
С	A 262	3360			A1 20070503					CA 2	006-		20061023							
E	P 194	3232			A1		2008	0716		EP 2	006-		20061023							
	R:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FΙ,	FR,	GB,	GR,	HU,	ΙE,			
		IS,	ΙT,	LI,	LT,	LU,	LV,	MC,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	ΑL,			
		BA,	HR,	MK,	RS															
PRIORI	PRIORITY APPLN. INFO.:								EP 2005-110080						A 20051027					
										WO 2006-EP67656						W 20061023				
OTHER	OTHER SOURCE(S):						MARPAT 146:482095													

AB Title compds. I [wherein X = N or CH; R1, R2 = H, alkyl, Ph, etc.;] or N-oxides, pharmaceutically acceptable salts and stereoisomers thereof were prepared as histone deacetylase (HDAC) inhibitors. For instance, successive condensation of 3,4-diethoxy-3-cyclobutene-1,2-dione with 3-aminobiphenyl and 2-(1-piperazinyl)pyrimidine-5-carboxylic acid Et ester, ester hydrolysis, condensation of the resultant acid with NH2O-THP, and deprotection with TFA gave hydroxamic acid II. This compds. showed inhibition against HDAC with pIC50 = 7.7. The invented compds. are useful for the treatment of proliferative diseases.

IT 935670-93-2P 935670-95-4P 935670-97-6P 935670-99-8P 935671-01-5P 935671-03-7P 935671-05-9P 935671-07-1P 935671-09-3P 935671-11-7P 935671-13-9P 935671-15-1P 935671-17-3P 935671-19-5P 935671-21-9P 935671-23-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of squaric acid derivs. as histone deacetylase (HDAC) inhibitors for treatment of proliferative diseases)

RN 935670-93-2 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-([1,1'-biphenyl]-3-ylamino)-3,4-dioxo-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935670-95-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[[[1-(phenylmethyl)-3-pyrrolidinyl]methyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy-(CA INDEX NAME)

RN 935670-97-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-(pentylamino)-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Me- (CH<sub>2</sub>) 
$$_4$$
-NH  $_{\rm N}$   $_{\rm N}$   $_{\rm N}$   $_{\rm C}$ 

RN 935670-99-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(1,2,3,4-tetrahydro-1-naphthalenyl)amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-01-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-[[2-(3-chlorophenoxy)ethyl]amino]-3,4-dioxo-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-03-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-[[3-(diethylamino)propyl]amino]-3,4-dioxo-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-05-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-[(2-furanylmethyl)amino]-3,4-dioxo-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-07-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-[[[1-(4-chlorophenyl)cyclopropyl]methyl]a mino]-3,4-dioxo-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ &$$

RN 935671-09-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(3-pyridinylmethyl)amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-11-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(2-phenylethyl)amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-13-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[[2-(2-pyridinyl)ethyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-15-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[[[3-(trifluoromethyl)phenyl]methyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-17-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[[(3,4,5-trimethoxyphenyl)methyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy-(CA INDEX NAME)

RN 935671-19-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[[2-(phenylamino)ethyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 935671-21-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[[3-(2-oxo-1-pyrrolidinyl)propyl]amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy-(CA INDEX NAME)

PAGE 1-A

PAGE 2-A

RN 935671-23-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3,4-dioxo-2-[(2-phenoxyethyl)amino]-1-cyclobuten-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

REFERENCE COUNT:

THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Erich Leese

<12/04/2007>

L11 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:101446 CAPLUS

DOCUMENT NUMBER: 144:192266

TITLE: Preparation of substituted propenyl piperazine

derivatives as novel inhibitors of histone deacetylase INVENTOR(S): Van Brandt, Sven Franciscus Anna; Van Emelen, Kristof;

Angibaud, Patrick Rene; Marconnet-Decrane, Laurence

APPLICATION NO.

DATE

Francoise Bernadette; Arts, Janine Janssen Pharmaceutica N.V., Belg.

PATENT ASSIGNEE(S): Janssen Pharmaceutica N. SOURCE: PCT Int. Appl., 67 pp.

CODEN: PIXXD2

KIND DATE

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.

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					A2 2006020. A3 2006060								20050725					
	W:	ΑE,	AG,	AL,	ΑM,	ΑT,	ΑU,	ΑZ,	ΒA,	BB,	ВG,	BR,	BW,	BY,	BZ,	CA,	CH,	
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FΙ,	GB,	GD,	
		GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	KM,	KP,	KR,	KΖ,	
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		NG,	NΙ,	NO,	NΖ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	
		SL,	SM,	SY,	ΤJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	
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CN	1993				A 20070704					CN 2	005-		20050725					
JP	2008	5082	34		T 20080321					JP 2	2007-		20050725					
BR	2005	0138	91		Α		2008	0520		BR 2	2005-		20050725					
KR	2007	0439	78		Α		2007	0426		KR 2	2007-		20070123					
US	2007	0135	424		A1		2007	0614		US 2	2007-	20070123						
IN	IN 2007DN00658						2007	0803			007-			0070	124			
	MX 200701119						2007				2007-		20070126					
	2007				А		2007	0227			2007-				20070227			
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Substituted propenyl piperazine derivs. I, wherein X is independently N or AB CH; R1 is Ph, naphthalenyl or heterocyclyl; wherein each of said Ph or naphthalenyl is optionally substituted with one or two substituents each independently selected from halo, alkyl, alkyloxy, poly-halo-alkyl, aryl, hydroxy, cyano, amino, alkylcarbonylamino, alkylsulfonylamino, hydroxycarbonyl, alkyloxycarbonyl, hydroxyalkyl, alkyloxymethyl, aminomethyl, alkylaminomethyl, alkylcarbonylaminomethyl, alkylsulfonylaminomethyl, aminosulfonyl, alkylaminosulfonyl or heterocyclyl; R2 is hydrogen, -CH2R5, trifluoromethyl, -C(0)-R6, or -CH-NR7R8; wherein each R5 is independently hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylcarbonyloxy, piperazinyl, N-methylpiperazinyl, morpholinyl, thiomorpholinyl, imidazolyl or triazolyl; each R6 is independently hydroxy, alkyloxy, amino or mono- or di(alkyl)amino, cycloalkylamino, hydroxyalkylamino, piperazinyl, N-methylpiperazinyl, morpholinyl or thiomorpholinyl; each R7 and R8 are independently hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, or mono- or di(alkyl)aminosulfonyl; R3 is hydrogen, hydroxymethyl, aminomethyl or mono- or di(alkyl)aminomethyl; R4 is hydrogen or alkyl; were prepared and having histone deacetylase inhibiting enzymic activity and to inhibit proliferative conditions, such as cancer and psoriasis. Thus, propenyl piperazine derivative II was prepared and tested in vitro and in nude mice as inhibitor of histone deacetylase and was better than R306465 after oral administration. P21 enzyme linked immunosorbent assay has been applied to determine the p21 protein expression level in human A2780 ovarian carcinoma cells. In vitro assay for inhibition of histone deacetylase is reported. P21 induction was measured as the consequence of DNA damage or as the consequence of histone deacetylase inhibition. Antiproliferative activity of title compds. was determined on A2780 cells (neg. log value of the IC50, pIC50 = 7.9-8.2).

TT 875138-85-5P 875138-87-7P 875138-88-8P 875138-89-9P 875138-90-2P 875138-91-3P 875138-93-5P 875138-94-6P 875138-98-0P 875139-00-7P 875139-02-9P 875139-04-1P 875139-06-3P 875139-07-4P 875139-09-6P 875139-11-0P 875139-13-2P 875139-14-3P 875139-15-4P 875139-17-6P 875139-19-8P 875139-20-1P 875139-21-2P 875139-23-4P 875139-24-5P 875139-25-6P 875139-26-7P 875139-27-8P 875139-30-3P 875139-31-4P 875139-69-8P

875139-70-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of substituted propenyl piperazine derivs. as novel inhibitors of histone deacetylase)

RN 875138-85-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875138-87-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-chlorophenyl)-1-(4-morpholinylmethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-86-6 CMF C23 H29 C1 N6 O3

$$\begin{array}{c|c} C1 & & & \\ & & \\ & & \\ CH = CH - CH - N & N & N \\ & & \\ & & \\ C-NH-OH \\ & \\ & \\ O \end{array}$$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875138-88-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.

RN 875138-89-9 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-88-8 CMF C19 H23 N5 O2

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

10/513699

RN 875138-90-2 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875138-91-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(acetyloxy)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875138-93-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(dimethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-92-4 CMF C22 H27 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875138-94-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(methoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875138-98-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methoxyphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-97-9 CMF C20 H25 N5 O4

Double bond geometry as shown.

CM 2

CRN 76-05-1

CMF C2 H F3 O2

RN 875139-00-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(2E)-3-(4-chlorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-99-1 CMF C19 H22 C1 N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-02-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-[1,1'-biphenyl]-4-yl-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-01-8 CMF C25 H27 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

$${\tiny \begin{array}{c}F\\F-C-CO_2H\\|\\F\end{array}}$$

RN 875139-04-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-03-0 CMF C20 H22 F3 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-06-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methylphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-05-2 CMF C20 H25 N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-07-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-methyl-1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-09-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(ethylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-08-5 CMF C23 H29 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-11-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(cyclopropylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-10-9 CMF C22 H26 N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-13-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[(methylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-12-1 CMF C20 H24 N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-14-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-15-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[[[2-(dimethylamino)ethyl]amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-17-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[[(2-hydroxyethyl)amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-16-5 CMF C21 H26 N6 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-19-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(butylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-18-7 CMF C25 H33 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-20-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-21-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-[(4-methyl-1-piperazinyl)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.

RN 875139-23-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(1H-imidazol-1-ylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-22-3 CMF C22 H25 N7 O2

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-24-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(ethoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-25-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1S)-1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

RN 875139-26-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1R)-1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

RN 875139-27-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1S)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry. Double bond geometry unknown.

RN 875139-28-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(3-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-29-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(2-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-30-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(methoxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-31-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1S)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-

propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

● HCl

RN 875139-69-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

RN 875139-70-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

● HCl

L11 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:300395 CAPLUS

DOCUMENT NUMBER: 142:355054

TITLE: Preparation of amide derivatives as inhibitors of

histone deacetylase

INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;

Frechette, Sylvie; Vaisburg, Arkadii; Besterman,

Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.

PATENT ASSIGNEE(S): Methylgene, Inc., Can. SOURCE: PCT Int. Appl., 559 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.													DATE 						
WO	2005030705 2005030705				A1			20050407											
	W: AE, AG, AL		AL,	AM,	ΑT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,			
								DK,											
		GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KP,	KR,	KΖ,	LC,		
		LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MΖ,	NA,	ΝI,		
		NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,		
		ΤJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW		
	RW:	BW,	GH,	GM,	ΚE,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,		
		ΑZ,	BY,	KG,	KΖ,	MD,	RU,	ТJ,	TM,	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,		
					•	•	•	HU,			•	•	•						
		SI,	SK,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	ΝE,		
		,	TD,																
	AU 2004276337																		
_	CA 2539117								CA 2004-2539117										
EP	1663																		
	R:	•		•	•			FR,			•		•		•				
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CN	1882	529			Α		2006	1220		CN 2	004-	8003	20040924						
														20040924					
														20060323					
	2008				А		2008	0424							20071030				
PRIORIT	RIORITY APPLN. INFO.:											5058							
												5329							
												5610							
												5282	-						
^=====================================	^ ~-	<i>(</i>			~		_ 1:	0 0=				US31			w 2	0040	924		
OTHER SO	THER SOURCE(S):					REAC	Т 14	Z <b>:</b> 35.	5054	; MA	KPAT	142	:355	054					

AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction The inhibitory

Ι

capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium] bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC 50 values in the range of below 1 up to 20  $\mu\text{M}$ . I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

IT 603985-82-6P 603985-86-0P 603985-88-2P 603985-90-6P 603985-94-0P 603991-95-3P 603991-96-4P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P 604784-81-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amide derivs. as inhibitors of histone deacetylase)

RN 603985-82-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(2-naphthalenylsulfonyl)-4-piperidinyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603985-86-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

$$HO-CH_2$$
 $O$ 
 $CH_2-N$ 
 $N$ 
 $C-NH-OH$ 

RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603985-94-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl])-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX

NAME)

RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[[(2-naphthalenylsulfonyl)amino]me thyl]-4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c}
O \\
S - NH - CH_2 \\
O \\
Ph - CH_2
\end{array}$$

$$\begin{array}{c|c}
N \\
N \\
N \\
O
\end{array}$$

$$\begin{array}{c}
C - NH - OH \\
O
\end{array}$$

REFERENCE COUNT:

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:300394 CAPLUS

DOCUMENT NUMBER: 142:373563

TITLE: Preparation of amide derivatives as inhibitors of

histone deacetylase

INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;

Frechette, Sylvie; Vaisburg, Arkadii; Besterman,

Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.

PATENT ASSIGNEE(S): Methylgene, Inc., Can. SOURCE: PCT Int. Appl., 389 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATE	KIN	D																
WO 2	WO 2005030704						2005		WO 2004-US31590									
Ţ	W:	ΑE,	AG,	AL,	AM,	ΑT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,	
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FΙ,	GB,	GD,	
		GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	KP,	KR,	KΖ,	LC,	
		LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NA,	NI,	
		NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,	
		ΤJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW	
]	RW:	BW,	GH,	GM,	ΚE,	LS,	MW,	MΖ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	
		AΖ,	BY,	KG,	KΖ,	MD,	RU,	ТJ,	TM,	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	
		EE,	ES,	FΙ,	FR,	GB,	GR,	HU,	ΙE,	IT,	LU,	MC,	NL,	PL,	PT,	RO,	SE,	
		SI,	SK,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	ML,	MR,	NE,	
		SN,	TD,	ΤG														
JP 2	0080	948	47		Α		2008	0424		JP 2	007-		20071030					
PRIORITY A	APPI	N.	INFO	.:						US 2	003-		P 20030924					
									US 2003-532973P						P 20031229			
										US 2	004-	5610	82P		P 2	0040	409	
										JP 2	006-	5282	79		A3 2	0040	924	
OTHER SOU	• •						CASREACT 142:373563; MARPAT 142:373563											

$$\begin{array}{c|c}
 & R^1 & R^2 \\
 & R^5 & R^3 \\
 & R^4 & R^4
\end{array}$$

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IT 603985-82-6P 603985-86-0P 603985-88-2P 603985-90-6P 603985-94-0P 603991-95-3P 603991-96-4P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P 604784-81-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

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 $O$ 
 $CH_2-N$ 
 $N$ 
 $C-NH-OH$ 

RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603985-94-0 CAPLUS

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NAME)

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CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[[(2-naphthalenylsulfonyl)amino]me thyl]-4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c}
O \\
S - NH - CH_2 \\
O \\
Ph - CH_2
\end{array}$$

$$\begin{array}{c|c}
N \\
N \\
N \\
O
\end{array}$$

$$\begin{array}{c}
C - NH - OH \\
O
\end{array}$$

REFERENCE COUNT:

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737757 CAPLUS

DOCUMENT NUMBER: 139:276911

TITLE: Preparation of N-(piperazinylmethyl-,

piperidinylmethyl- and morpholinylmethyl) sulfonamides and amides as novel inhibitors of histone deacetylase

and amides as novel innibitors of his

INVENTOR(S): Van Emelen, Kristof

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 69 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

PA:	TENT	NO.			KIND DATE					APP	LICAT	ION :		DATE				
WO	2003	0764	38								2003-					0030	311	
	W:	CO, GM,	CR, HR,	CU, HU,	CZ, ID,	DE, IL,	DK, IN,	DM, IS,	DZ, JP,	EC KE	B, BG, E, EE, E, KG, I, MW,	ES, KP,	FI, KR,	GB, KZ,	GD, LC,	GE, LK,	GH, LR,	
		PL, UA,	PT, UG,	RO, US,	RU, UZ,	SC, VC,	SD, VN,	SE, YU,	SG, ZA,	SK ZM	I, SL, I, ZW	TJ,	TM,	TN,	TR,	TT,	TZ,	
	R₩:	KG, FI,	KZ, FR,	MD, GB,	RU, GR,	TJ, HU,	TM, IE,	AT, IT,	BE,	BG MC	TZ, G, CH,	CY, PT,	CZ, RO,	DE, SE,	DK, SI,	EE, SK,	ES, TR,	
CA	2475										9, GW, 2003-							
EP							2004	1215		AU EP	2003- 2003-	2187 7119	20030311 20030311					
EP	1485 R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,			I, IT,						PT,	
BR CN	2003 1642 2005							1221	·	BR	2003- 2003- 2003-	7606	·	·	2	0030	311 311	
NZ	5348	33			A		2006	0728		NZ	2003-	5348	33		2	0030.	311	
AT	1010 3986 2836	15			A T B		2007 2008 2007	0715		ΑT	2007- 2003- 2003-	7119		311				
IN	IN 2004DN02536										2004-	DM25		20040831				
ИО	MX 2004PA08795 NO 2004004135 CORITY APPLN. INFO.:				A 20041126 A 20040929					MX 2004-PA8795 NO 2004-4135 US 2002-363799P					20040910 20040929			
										WO CN	2002- 2003- 2003-	EP14 8059	833 21		A 2 A3 2	0021	223 311	
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OTHER SOURCE(S): MARPAT 139:276911

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$$\begin{array}{c|c}
R^{2} & CH_{2} \\
\downarrow & L - A \\
\downarrow & Z
\end{array}$$

The title compds. [I; t = 0-4; Q, X, Y = N, C; Z = NH, O, CH2; R1 = CONR3R4, NHCOR7, CO(alkanediyl)SR7, etc. (wherein R3, R4 = H, OH, alkyl, etc.; R7 = H, alkyl, alkylcarbonyl, etc.); R2 = H, OH, NH2, etc.; L = NR9CO, NR9SO2, NR9CH2 (R9 = H, alkyl, cycloalkyl, etc.); A = (un)substituted Ph, cycloalkyl, pyridyl, etc.], having histone deacetylase inhibiting enzymic activity, were prepared and formulated. E.g., a multi-step synthesis of (+)-II which showed pIC50 of 7.723 against HDAC, was given.

IT 604784-81-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of N-(piperazinylmethyl-, piperidinylmethyl- and morpholinylmethyl) sulfonamides and amides as novel inhibitors of histone deacetylase)

RN 604784-81-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[3-[[(2-naphthalenylsulfonyl)amino]me thyl]-4-(phenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} O \\ S - NH - CH_2 \\ O \\ Ph - CH_2 \\ \end{array}$$

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737723 CAPLUS

DOCUMENT NUMBER: 139:261309

TITLE: Preparation of N-hydroxy-5-piperazino(piperidino or

diazepino) - 2 - pyrimidine carboxamides and

N-hydroxy-4-piperazino(piperidino or

diazepino) benzamides as new inhibitors of histone

deacetylase

INVENTOR(S): Angibaud, Patrick Rene; Pilatte, Isabelle Noeelle

Constance; Van Brandt, Sven Franciscus Anna; Roux, Bruno; Ten Holte, Peter; Verdonck, Marc Gustaaf

Celine; Meerpoel, Lieven; Dyatkin, Alexey Borisovich

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 72 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

PA:									APPLICATION NO.									
WO	2003																0030	311
	W:	ΑE,	AG,	AL,	AM,	ΑT,	AU,	AZ,	BA,	BE	3, B	ЗG,	BR,	BY,	BZ,	CA,	CH,	CN,
		CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	ΕC	), E	Œ,	ES,	FΙ,	GB,	GD,	GE,	GH,
		GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE	Ξ, Κ	ζG,	KP,	KR,	KΖ,	LC,	LK,	LR,
		LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN	J, M	ΊW,	MX,	MZ,	NO,	NΖ,	OM,	PH,
		PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK	<, S	SL,	ТJ,	TM,	TN,	TR,	TT,	TZ,
		UA,	UG,	US,	UΖ,	VC,	VN,	YU,	ZA,	ZM	1, Z	ZW						
	RW:						MZ,											
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		FΙ,	FR,	GB,	GR,	HU,	ΙE,	ΙΤ,	LU,	MC	), N	IJΙ,	PT,	RO,	SE,	SI,	SK,	TR,
		BF,	ВJ,			CI,	CM,	GΑ,	GN,	GÇ	), G	₩,	ML,	MR,	NE,	SN,	TD,	ΤG
CA 2475764					A1		2003	0918	CA 2003-2475764 AU 2003-218736 EP 2003-711980							2003031		
AU	2003	2187	36		A1 A1 A1		2003	0922		AU	200		2	0030	311			
EP	1485						2004	1215		EΡ	200	3-	7119	80		2	0030	311
	R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GF	R, I	ΙΤ,	LI,	LU,	NL,	SE,	MC,	PT,
		ΙE,	SI,	LT,	LV,		RO,										SK	
BR	2003	0800	81		Α		2004	1221		BR	200	3-8	3081			2	0030	311
CN	1639: 1642: 5348: 2005:	125			Α		2005	0713	1	CN	200	3-8	3056	75		2	0030	311
CN	1642	551			Α		2005	0/20		CN	200	)	8058.	33		2	0030	311
NZ	53483	34			Α		2005	0729		NZ	200	3-!	5348				0030	311
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CN	1010	0780	3		Α		2007	0801						5212			0030	311
ΙN	20041	DN02			A		2007							33			0040	831
US	2005	0107	384		A1		2005	0519		US	200	4 - 5	50699	98		2	0040	908
ZA	2004	0072	37		Α		2005	0928					_				0040	909
ZA	2004	0072	35		Α		2005	1004									0040	909
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ZA	2004	0072	33		Α		2005	1006		ZA	200	4-	7233			2	0040	909
	2004						2005	1006		ZA	200	) 4 – '	7234			2	0040	909
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	20041				Α		2004	1126		MX	200	)4-1	PA88	06		2	0040	910
NO 2004004194					Α		2004	1001					4194				0041	
)RIT	Y APP	LN.	INFO	.:													0020	
																A 2	0021	223
									1	CN	200	3-8	3059	21		A3 2	0030	311

WO 2003-EP2514 W 20030311

OTHER SOURCE(S): MARPAT 139:261309

GΙ

AB The title compds. [I; n = 0-3; t = 0-4; Q, X, Y = N, C; Z = N, CH; R1 = CONR7R8, NHCOR9, CO(alkanediyl)SR9, etc. (wherein R7, R8 = H, OH, alkyl, etc.; R9 = H, alkyl, alkylcarbonyl, etc.); R2 = H, halo, OH, etc.; L = a bond, alkanediyl, alkanediyloxy, NH, CO, NHCO; each R3 = H and one H atom can be replaced by aryl; R4 = H, OH, NH2, etc.; A = (un)substituted Ph, cyclohexyl, pyridyl, etc.], having histone deacetylase inhibiting enzymic activity, were prepared and formulated. E.g., a multi-step synthesis of II which showed pIC50 of 5.121 against HDAC, was given.

ΙI

IT 603985-83-7P 603985-87-1P 603985-89-3P 603985-91-7P 603985-95-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of piperazino(piperidino or diazepino) substituted 2-pyrimidinecarbohydroxamic acids and N-hydroxybenzamides as new inhibitors of histone deacetylase)

RN 603985-83-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(2-naphthalenylsulfonyl)-4-piperidinyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (10:9) (CA INDEX NAME)

CM 1

CRN 603985-82-6 CMF C24 H28 N6 O4 S

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-87-1 CAPLUS

5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-86-0 CMF C21 H23 N5 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

<12/04/2007>

RN 603985-89-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-88-2 CMF C20 H21 N5 O2

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-91-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-90-6 CMF C21 H23 N5 O2

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-95-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:2) (CA INDEX NAME)

CM 1

CRN 603985-94-0 CMF C25 H30 N6 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

REFERENCE COUNT:

3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737586 CAPLUS

DOCUMENT NUMBER: 139:261308

TITLE: Preparation of anyl and heteroaryl hydroxamic acids as

inhibitors of histone deacetylase for treating

proliferative diseases

INVENTOR(S): Van Emelen, Kristof; Verdonck, Marc Gustaaf Celine;

Van Brandt, Sven Franciscus Anna; Angibaud, Patrick Rene; Meerpoel, Lieven; Dyatkin, Alexey Borisovich

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 52 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

	TENT								APP]	LICAT	ION 1		DATE				
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					147.51			0.04.0		WO 2	2003-	EP25	15		W 2	20030	311

OTHER SOURCE(S): MARPAT 139:261308

GΙ

AΒ This invention comprises aryl and heteroaryl hydroxamic acids (shown as I; variables defined below; e.g. II) having histone deacetylase inhibiting enzymic activity; their preparation, compns. containing them and their use as a medicine. Compds. I show excellent in-vitro histone deacetylase inhibiting enzymic activity, have advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity), and show good metabolic stability and high bioavailability and more particular show oral bioavailability. They can also be used for detection and identification of histone deacetylase. General synthetic procedures and characterization data for twenty-seven I are included; also, prepns. of 12 intermediates are included. For example, a 59 % yield of 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5-carbohydroxamic acid was obtained by removing the O-tetrahydropyranyl group of its ester using trifluoroacetic acid; the ester was prepared in 61 % yield from N'-(ethylcarbonimidoyl)-N,N-dimethyl-1,3-propanediamine monohydrochloride, sodium 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5carboxylate, O-(tetrahydro-2H-pyran-2-yl)hydroxylamine, and 1-hydroxy-1H-benzotriazole in CH2Cl2/THF. The sodium salt was obtained by base hydrolysis of the Et ester; the ester was prepared in 73 % yield from Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate and dimethylsulfamoyl chloride; Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate was obtained in <96 % yield from Et 2-(4-benzylpiperazin-1-yl)pyrimidine-5-carboxylate by hydrogenation using Pd/C; the benzyl derivative was obtained from 1-(phenylmethyl)piperazine, (135 mL) was added gradually to a solution of potassium carbonate (0.18 mol) and 2-(methylsulfonyl)-5pyrimidinecarboxylic acid Et ester, K2CO3 in MeCN. For I: n is 0-3; Q, X and Y are N or C; Z is N or CH; R1 is -C(0)NR5R6, -N(H)C(0)R7, -C(0)-C1-6alkanediylSR7, -NR8C(0)N(OH)R7, -NR8C(0)C1-6alkanediylSR7, -NR8C(O)C:N(OH)R7 or another Zn-chelating-group; R2 is H, halo, hydroxy, amino, nitro, C1-6alkyl, C1-6alkyloxy, trifluoromethyl, di(C1-6-alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl. R3 is H, C1-6-alkyl, arylC2-6alkenediyl, furanylcarbonyl, naphthalenylcarbonyl, -C(0)phenylR9, C1-6alkylaminocarbonyl, aminosulfonyl, arylaminosulfonyl, aminosulfonylamino, di (C1-6-alkyl) aminosulfonylamino, arylaminosulfonylamino, aminosulfonylaminoC1-6-alkyl, di(C1-6alkyl)aminosulfonylaminoC1-6-alkyl, arylaminosulfonylaminoC1-6alkyl, di(C1-6-alkyl)aminoC1-6alkyl, C11-12-alkylsulfonyl, di(C1-6alkyl)aminosulfonyl, trihaloC1-6-alkylsulfonyl, di(aryl)C1-6alkylcarbonyl, thiophenylC1-6alkylcarbonyl, pyridinylcarbonyl or arylC1-6alkylcarbonyl. R4 is H, hydroxy, amino, hydroxyC1-6alkyl, C1-6alkyl, C1-6alkyloxy,

arylC1-6alkyl, aminocarbonyl, hydroxycarbonyl, aminoC1-6-alkyl, aminocarbonylC1-6-alkyl, hydroxycarbonylC1-6-alkyl, hydroxyaminocarbonyl, C1-6-alkyloxycarbonyl, C1-6-alkylaminoC1-6-alkyl or di(C1-6-alkyl)aminoC1-6-alkyl; when R3 and R4 are present on the same C atom, R3 and R4 together may form -C(0)-NH-CH2-NR10- wherein R10 is H or aryl; when R3 and R4 are present on adjacent C atoms, R3 and R4 together may form :CH-CH:CH-CH:; addnl. details are given in the claims.

IT 603991-96-4P

RL: ARG (Analytical reagent use); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

IT 603991-95-3P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P

RL: ARG (Analytical reagent use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} S & CH_2-C-N & N & N \\ \hline \\ C-NH-OH \\ \hline \\ O & \\ \end{array}$$

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

REFERENCE COUNT:

6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

## => file erg

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		ENTRY	SESSION
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<12/04/2007>

Erich Leese

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chain nodes :
10 11 20 21 22 23 24 25 27 28 29 30 31 32 33 34 35
ring nodes :
1 2 3 4 5 14 15 16 17 18 19 26
chain bonds :
1-27 \quad 1-28 \quad 2-18 \quad 3-33 \quad 3-34 \quad 4-10 \quad 5-29 \quad 5-30 \quad 10-11 \quad 15-20 \quad 16-35 \quad 20-21 \quad 20-22
22-23 22-24 23-25 26-31 26-32
ring bonds :
1-2 1-5 2-3 3-26 4-5 4-26 14-15 14-19 15-16 16-17 17-18 18-19
exact/norm bonds :
1-2 \quad 1-5 \quad 2-3 \quad 2-18 \quad 3-26 \quad 4-10 \quad 4-5 \quad 4-26 \quad 10-11 \quad 20-21 \quad 20-22 \quad 22-23
exact bonds :
1-27 \quad 1-28 \quad 3-33 \quad 3-34 \quad 5-29 \quad 5-30 \quad 15-20 \quad 16-35 \quad 22-24 \quad 23-25 \quad 26-31 \quad 26-32
normalized bonds :
14-15 14-19 15-16 16-17 17-18 18-19
isolated ring systems :
containing 1 :
G1:C,N
G2:Ak, NH2, NO2
G3:0
G4
G5:C,N,Zn,H
Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 10:CLASS 11:Atom 14:Atom 15:Atom
16:Atom 17:Atom 18:Atom 19:Atom 20:CLASS 21:CLASS 22:CLASS 23:CLASS
24:CLASS 25:CLASS 26:Atom 27:CLASS 28:CLASS 29:CLASS 30:CLASS 31:CLASS
32:CLASS 33:CLASS 34:CLASS 35:CLASS
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## L12 STRUCTURE UPLOADED

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FULL SEARCH INITIATED 16:08:56 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 1679 TO ITERATE

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<12/04/2007>

L14 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:353001 CAPLUS

DOCUMENT NUMBER: 148:355828

TITLE: Multi-functional small molecules as anti-proliferative

agents and their preparation

INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen; Zhai,

Haixiao

PATENT ASSIGNEE(S): Curis, Inc., USA

SOURCE: PCT Int. Appl., 494pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA	PATENT NO.					D	DATE		-	APPL	ICAT		DATE 				
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	W:						AU,		BA,	BB,	BG,	BH,	BR,	BW,	BY,	BZ,	CA,
		•					CZ,			•	,						
		GB,	GD,	GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,
		KM,	KN,	KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LY,	MA,	MD,	ME,
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OTHER SOURCE(S): MARPAT 148:355828

GΙ

$$A-B-C$$
 I MeO N II

AB The invention relates to the compns., methods, and applications of an approach to selective inhibition of several cellular or mol. targets with a single small mol. More specifically, the present invention relates to multi-functional small mols. of formula I wherein one functionality is capable of inhibiting histone deacetylases (HDAC) and the other functionality is capable of inhibiting a different cellular or mol. pathway involved in aberrant cell proliferation, differentiation or

survival. Compds. of formula I wherein A is a pharmacophore of an anticancer agent capable of inhibiting at least one cellular or mol. pathway involved in the aberrant cell proliferation, differentiation or survival; B is a linker; C is a zinc-binding moiety; and their geometrical isomers, enantiomers, diastereoisomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, are claimed. Example compound II was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their antiproliferative activity (some data given).

IT 1011716-90-7P

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRPH (Prophetic); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prophetic starting material; preparation of multi-functional small mols. as antiproliferative agents)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[4-[[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

L14 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2008:351928 CAPLUS

DOCUMENT NUMBER: 148:355814

TITLE: Preparation of (aralkylamino)(phenyl)pyrrolo[2,3-d]pyrimidine derivatives for use as protein tyrosine

kinase (PTK) inhibitors

INVENTOR(S): Cai, Xiong; Qian, Changgeng; Gould, Stephen

PATENT ASSIGNEE(S): Curis, Inc., USA

SOURCE: PCT Int. Appl., 123pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

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		GH,	GM,	KΕ,	LS,	MW,	MZ,	NΑ,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	ΑM,	ΑZ,
		BY,	KG,	KΖ,	MD,	RU,	ТJ,	$_{ m TM}$									
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PRIORIT	PRIORITY APPLN. INFO.:									US 2	006-	8436	46P		P 2	0060	911
										US 2	007-	89589	94P		P 2	0070	320
OTHER S	THER SOURCE(S):						MARPAT 148:355814										

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Fused bicyclic pyrimidine derivs. I and II [Ar = aryl, substituted arylheteroaryl or heteroaryl; Q = absent or (un)substituted alkyl; X = 0, S, NH, or alkylamino; Z = 0, S, NR1; Y = N or CR2; B = linker; D = C(0)NH2, NHC(S)CH3, CHC(0)NHacyl, etc.; R1 = H or (un)substituted alkyl; R2 = H, halo, (un)substituted aliphatic, aryl or heteroaryl], and their pharmaceutically acceptable salts, are prepared and disclosed as protein tyrosine kinase (PTK) inhibitors. Thus, e.g., III was prepared by N-alkylation of 1,4-dioxa-8-azaspiro[4.5]decane with 6-(4- (chloromethyl)phenyl)-N-((R)-1-phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (preparation given) and deprotection followed by condensation with 6-aminohexanoic acid Me ester and amidation with hydroxylamine. Select I were evaluated in EGFR assays, e.g., III demonstrated an IC50 value of  $\leq 0.1~(\mu M)$ .

IT 1011716-90-7P

GI

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)

(preparation of (aralkylamino)(phenyl)pyrrolopyrimidine derivs. for use as protein tyrosine kinase (PTK) inhibitors)

RN 1011716-90-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[4-[4-[[(1R)-1-phenylethyl]amino]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

L14 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:816930 CAPLUS

DOCUMENT NUMBER: 147:211903

TITLE: Preparation of pyrimidine derivatives as histone

deacetylase inhibitors

INVENTOR(S): Marconnet-Decrane, Laurence Francoise Bernadette;

Gaurrand, Sandrine Francoise Dominique; Angibaud,

Erich Leese

Patrick Rene

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 62pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

	PATENT 1	NO.			KIN	D	DATE		APPLICATION NO.							DATE 		
	WO 2007	0828	 74		A1	_	2007	0726		 WO 2	007-	 EP50	 371		2	0070	 116	
	W:	ΑE,	AG,	AL,	AM,	ΑT,	ΑU,	ΑZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,	
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,	
		GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	KM,	KN,	
		KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	LY,	MA,	MD,	MG,	MK,	
		MN,	MW,	MX,	MΥ,	MZ,	NA,	NG,	ΝI,	NO,	NΖ,	OM,	PG,	PH,	PL,	PT,	RO,	
		RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ТJ,	TM,	TN,	TR,	ΤT,	
		TZ,	UA,	UG,	US,	UΖ,	VC,	VN,	ZA,	ZM,	ZW							
	RW:	ΑT,	ΒE,	ВG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FΙ,	FR,	GB,	GR,	HU,	ΙE,	
		IS,	ΙT,	LT,	LU,	LV,	MC,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,	ВJ,	
		CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	$ ext{ML}$ ,	MR,	ΝE,	SN,	TD,	ΤG,	BW,	GH,	
		GM,	KΕ,	LS,	MW,	${ m MZ}$ ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	ΑM,	ΑZ,	BY,	
		KG,	KZ,	MD,	RU,	ТJ,	$_{ m TM}$											
	CA 2630717				A1 20070726				CA 2007-2630717						2	0070	116	
PRIOR	RIORITY APPLN. INFO.:			.:						EP 2	006-	1005	70		A 2	0060	119	
										WO 2	007-	EP50	371	,	W 2	0070	116	
OMITTOD	MILED COLLDON (C)						1 1 7	0110	^ ^									

OTHER SOURCE(S): MARPAT 147:211903

GΙ

<12/04/2007>

AB The title compds. with general formula I [wherein R1 = OH or substituted phenyl; X = N or CH; R2 = amino, alkylamino, alkoxyl, OH, etc.; R3 = (un)substituted Ph, naphthalene, or heterocycle] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC50 values of 7.0 and 5.3, resp. Formulations containing I as active ingredients were also reported.

IT 944738-91-4P 944738-94-7P 944738-97-0P

944739-00-8P 944739-08-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of pyrimidine derivs. as histone deacetylase inhibitors)

RN 944738-91-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(acetylamino)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-90-3 CMF C21 H26 N6 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

<12/04/2007>

RN 944738-94-7 CAPLUS
CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-amino-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-93-6
CMF C19 H24 N6 O2

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944738-97-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(2,5-dioxo-1-pyrrolidinyl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-96-9 CMF C23 H26 N6 O4

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944739-00-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(4-fluorophenoxy)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944738-99-2 CMF C25 H26 F N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944739-08-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(3E)-2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-4-phenyl-3-buten-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944739-07-5 CMF C27 H26 N6 O4

Double bond geometry as shown.

CM 2

<12/04/2007>

10/513699

CRN 76-05-1 CMF C2 H F3 O2

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:816806 CAPLUS

DOCUMENT NUMBER: 147:211902

TITLE: Preparation of pyrimidine derivatives as histone

deacetylase inhibitors

INVENTOR(S): Angibaud, Patrick Rene; Van Brandt, Sven Franciscus

Anna; Marconnet-Decrane, Laurence Francoise

Bernadette; Roux, Bruno

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 63pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

GΙ

PA	PATENT NO.					D	DATE		APPLICATION NO.							DATE			
WO	2007	0828	80		A1		2007	0726		——— WO 2	 007-:	EP50:	 379		2	0070:	116		
	W:	ΑE,	AG,	AL,	AM,	ΑT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,		
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,		
		GE,	GH,	GM,	GT,	HN,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KM,	KN,		
		KP,	KR,	KΖ,	LA,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	LY,	MA,	MD,	MG,	MK,		
		MN,	MW,	MX,	MY,	MZ,	NA,	NG,	ΝI,	NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,		
		RS,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,	SV,	SY,	ΤJ,	TM,	TN,	TR,	TT,		
		TZ,	UA,	UG,	US,	UZ,	VC,	VN,	ZA,	ZM,	ZW								
	RW:	AT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	ΙE,		
		IS,	IT,	LT,	LU,	LV,	MC,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,	ВJ,		
		•	•	•	•	•	GN,	•	•	•	•	•	•	•	•	•	•		
		GM,	KE,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	AZ,	BY,		
		KG,	KΖ,	MD,	RU,	ΤJ,	TM	•	•	·	•	•	·	,	·	,	•		
PRIORITY	ORITY APPLN. INFO.:				, 1.0, 10, 11			EP 2006-100571						i	A 20060119				
OTHER SOURCE(S):																			
GT																			

The title compds. with general formula I [wherein R1 = OH or substituted AB phenyl; R2 = -CH2OH, -CH2OCH3, -CH2OCH2CH3, or -CH2CH(OH)CH2OH; T = N(R3), where R3 = H, alkyl, cycloalkyl, etc.; X = N or CH; Y = O, NH, CH2, etc.; n = 0-1; p = 0-1, provided that when p = 0 then n = 0 and Y = N, and -CH(R2)-Z is attached to Y; Z = (un) substituted aryl or heteroaryl] or N-oxide forms, pharmaceutically acceptable salts, or stereoisomeric forms thereof were prepared as histone deacetylase (HDAC) inhibitors for the treatment of proliferative diseases. For example, compound II was prepared in a multi-step synthesis. In vitro assay for inhibition of HDAC was performed to measure the inhibition of HDAC enzymic activity, and colorimetric assay was performed to determine cellular activity on A2780 tumor cells. II showed HDAC inhibitory and anti-proliferative activities in the above two assays with pIC50 values of 7.0 and 7.1, resp. Formulations containing I as active ingredients were also reported. ΙT 944712-03-2P 944712-05-4P 944712-07-6P 944712-09-8P 944712-10-1P 944712-12-3P 944712-14-5P 944712-16-7P 944712-18-9P RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (drug candidate; preparation of pyrimidine derivs. as histone deacetylase

inhibitors)

944712-03-2 CAPLUS RN

5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(1-CN naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-02-1 CMF C21 H23 N5 O3

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

$$\begin{array}{c} F \\ | \\ F - C - CO_2H \\ | \\ F \end{array}$$

RN 944712-05-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-2-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-04-3 CMF C19 H21 N5 O3 S

CM 2

10/513699

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-07-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-[1-(phenylsulfonyl)-1H-indol-3-yl]ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-06-5 CMF C25 H26 N6 O5 S

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-09-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-

<12/04/2007>

dihydroxypropyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 944712-10-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 944712-09-8 CMF C22 H31 N5 O4

$$\begin{array}{c|c} O & OH \\ HO-CH_2-CH \\ N & N-CH \end{array}$$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-12-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R,2S)-1-[4-(1,1-dimethylethyl)phenyl]-2,3-dihydroxypropyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-11-2 CMF C22 H31 N5 O4

Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-14-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-hydroxy-1-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 944712-13-4 CMF C21 H23 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-16-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(2-benzofuranyl)-2-hydroxyethyl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

CM 1

CRN 944712-15-6 CMF C19 H21 N5 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 944712-18-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(1-benzo[b]thien-3-yl-2-hydroxyethyl)-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:?) (CA INDEX NAME)

Erich Leese

CM 1

CRN 944712-17-8 CMF C19 H21 N5 O3 S

<12/04/2007>

CM 2

CRN 76-05-1 CMF C2 H F3 O2

REFERENCE COUNT:

3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:101446 CAPLUS

DOCUMENT NUMBER: 144:192266

TITLE: Preparation of substituted propenyl piperazine

derivatives as novel inhibitors of histone deacetylase INVENTOR(S):

Van Brandt, Sven Franciscus Anna; Van Emelen, Kristof;

Angibaud, Patrick Rene; Marconnet-Decrane, Laurence

Francoise Bernadette; Arts, Janine Janssen Pharmaceutica N.V., Belg.

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., SOURCE: PCT Int. Appl., 67 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

GΙ

PA'	TENT	NO.			KIND DATE				APPL	ICAT		DATE								
					A2 2006 A3 2006			0202		WO 2	005-	EP53	611		2	0050	725			
	₩:	CN, GE, LC,	CO, GH, LK,	CR, GM, LR,	CU, HR, LS,	CZ, HU, LT,	AU, DE, ID, LU, PG,	DK, IL, LV,	DM, IN, MA,	DZ, IS, MD,	EC, JP, MG,	EE, KE, MK,	EG, KG, MN,	ES, KM, MW,	FI, KP, MX,	GB, KR, MZ,	GD, KZ, NA,			
	Dia.	ZA,	ZM,	ZW	·		TN,	·	·	·		·	·	·						
	KW:	IS, CF, GM,	IT, CG, KE,	LT, CI, LS,	LU, CM, MW,	LV, GA, MZ,	CZ, MC, GN, NA,	NL, GQ,	PL, GW,	PT, ML,	RO, MR,	SE, NE,	SI, SN,	SK, TD,	TR, TG,	BF, BW,	BJ, GH,			
CA	KG, KZ, MD, 2005266311 2572971				A1 20060202					CA 2	005-	2572		20050725 20050725						
		AT, IS,	BE,	BG, LI,	CH, LT,	CY,	CZ, LV,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,					
JP BR KR US IN MX	1993 2008 2005 2007 2007 2007 2007 Y APP	356 5082 0138 0439 0135 DN00 0111 0011	34 91 78 424 658 9		A T A A A1 A			0321 0520 0426 0614 0803 0315		JP 2 BR 2 KR 2 US 2 IN 2 MX 2 NO 2 EP 2 US 2	007- 005- 007- 007- 007- 007- 004- 004-		20070123 20070123 20070124 20070126 20070227 A 20040728 P 20040729							
OTHER S							T 14	4:19	WO 2005-EP53611 W 20050725 CASREACT 144:192266; MARPAT 144:192266											

$$\begin{array}{c|c} & & & & & & & & & & & & & & & & \\ & & & & & & & & & & & & & & \\ & & & & & & & & & & & & \\ & & & & & & & & & & & \\ & & & & & & & & & & \\ & & & & & & & & & \\ & & & & & & & & & \\ & & & & & & & & \\ & & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & & \\ & & & \\ & \\ & & \\ &$$

Substituted propenyl piperazine derivs. I, wherein X is independently N or AB CH; R1 is Ph, naphthalenyl or heterocyclyl; wherein each of said Ph or naphthalenyl is optionally substituted with one or two substituents each independently selected from halo, alkyl, alkyloxy, poly-halo-alkyl, aryl, hydroxy, cyano, amino, alkylcarbonylamino, alkylsulfonylamino, hydroxycarbonyl, alkyloxycarbonyl, hydroxyalkyl, alkyloxymethyl, aminomethyl, alkylaminomethyl, alkylcarbonylaminomethyl, alkylsulfonylaminomethyl, aminosulfonyl, alkylaminosulfonyl or heterocyclyl; R2 is hydrogen, -CH2R5, trifluoromethyl, -C(0)-R6, or -CH-NR7R8; wherein each R5 is independently hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylcarbonyloxy, piperazinyl, N-methylpiperazinyl, morpholinyl, thiomorpholinyl, imidazolyl or triazolyl; each R6 is independently hydroxy, alkyloxy, amino or mono- or di(alkyl)amino, cycloalkylamino, hydroxyalkylamino, piperazinyl, N-methylpiperazinyl, morpholinyl or thiomorpholinyl; each R7 and R8 are independently hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, or mono- or di(alkyl)aminosulfonyl; R3 is hydrogen, hydroxymethyl, aminomethyl or mono- or di(alkyl)aminomethyl; R4 is hydrogen or alkyl; were prepared and having histone deacetylase inhibiting enzymic activity and to inhibit proliferative conditions, such as cancer and psoriasis. Thus, propenyl piperazine derivative II was prepared and tested in vitro and in nude mice as inhibitor of histone deacetylase and was better than R306465 after oral administration. P21 enzyme linked immunosorbent assay has been applied to determine the p21 protein expression level in human A2780 ovarian carcinoma cells. In vitro assay for inhibition of histone deacetylase is reported. P21 induction was measured as the consequence of DNA damage or as the consequence of histone deacetylase inhibition. Antiproliferative activity of title compds. was determined on A2780 cells (neg. log value of the IC50, pIC50 = 7.9-8.2).

TT 875138-85-5P 875138-87-7P 875138-88-8P 875138-89-9P 875138-90-2P 875138-91-3P 875138-93-5P 875138-94-6P 875138-98-0P 875139-00-7P 875139-02-9P 875139-04-1P 875139-06-3P 875139-07-4P 875139-09-6P 875139-11-0P 875139-13-2P 875139-14-3P 875139-15-4P 875139-17-6P 875139-19-8P 875139-20-1P 875139-21-2P 875139-23-4P 875139-24-5P 875139-25-6P 875139-26-7P 875139-27-8P 875139-30-3P 875139-31-4P 875139-69-8P

875139-70-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of substituted propenyl piperazine derivs. as novel inhibitors of histone deacetylase)

RN 875138-85-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875138-87-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-chlorophenyl)-1-(4-morpholinylmethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-86-6 CMF C23 H29 C1 N6 O3

$$\begin{array}{c|c} C1 & & & \\ & & \\ & & \\ CH = CH - CH - N & N & N \\ & & \\ & & \\ C-NH-OH \\ & \\ & \\ O \end{array}$$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875138-88-8 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.

RN 875138-89-9 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-methyl-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-88-8 CMF C19 H23 N5 O2

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

10/513699

RN 875138-90-2 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875138-91-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(acetyloxy)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875138-93-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(dimethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-92-4 CMF C22 H27 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875138-94-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(methoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875138-98-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methoxyphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-97-9 CMF C20 H25 N5 O4

Double bond geometry as shown.

CM 2

CRN 76-05-1

CMF C2 H F3 O2

RN 875139-00-7 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(2E)-3-(4-chlorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875138-99-1 CMF C19 H22 C1 N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-02-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-[1,1'-biphenyl]-4-yl-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-01-8 CMF C25 H27 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-04-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-03-0 CMF C20 H22 F3 N5 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-06-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-(hydroxymethyl)-3-(4-methylphenyl)-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-05-2 CMF C20 H25 N5 O3

Double bond geometry as shown.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-07-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-methyl-1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-09-6 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(ethylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-08-5 CMF C23 H29 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-11-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(cyclopropylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-10-9 CMF C22 H26 N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-13-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[(methylamino)carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-12-1 CMF C20 H24 N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-14-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylcarbonyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-15-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[[[2-(dimethylamino)ethyl]amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-17-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-[[(2-hydroxyethyl)amino]carbonyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-16-5 CMF C21 H26 N6 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-19-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-[(butylmethylamino)carbonyl]-3-(4-fluorophenyl)-1-methyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-18-7 CMF C25 H33 F N6 O3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-20-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(4-morpholinylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

RN 875139-21-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(2E)-1-[(4-methyl-1-piperazinyl)methyl]-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Double bond geometry as shown.

RN 875139-23-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[1-(1H-imidazol-1-ylmethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 875139-22-3 CMF C22 H25 N7 O2

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 875139-24-5 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[1-(ethoxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-25-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1S)-1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

RN 875139-26-7 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[(1R)-1-(hydroxymethyl)-3-phenyl-2-propen-1-yl]-1-piperazinyl]- (CA INDEX NAME)

Absolute stereochemistry. Double bond geometry unknown.

RN 875139-27-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1S)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry. Double bond geometry unknown.

RN 875139-28-9 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(3-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-29-0 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(2-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-30-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[3-(4-fluorophenyl)-1-(methoxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 875139-31-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1S)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-

propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

● HCl

RN 875139-69-8 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

RN 875139-70-1 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[(1R)-3-(4-fluorophenyl)-1-(hydroxymethyl)-2-propen-1-yl]-1-piperazinyl]-N-hydroxy-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

● HCl

L14 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:300395 CAPLUS

DOCUMENT NUMBER: 142:355054

TITLE: Preparation of amide derivatives as inhibitors of

histone deacetylase

INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;

Frechette, Sylvie; Vaisburg, Arkadii; Besterman,

Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.

PATENT ASSIGNEE(S): Methylgene, Inc., Can. SOURCE: PCT Int. Appl., 559 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PA:	KIN	D	DATE			APPL	ICAT	ION 1		DATE													
							0050407 WO 2004-US31591 20							0040924									
	W:	CN,	CO,	CR,	CU,	CZ,	AU, DE, ID,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,						
		NO,	NZ,	OM,	PG,	PH,	LV, PL, TZ,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,						
	RW:	BW, AZ,	GH, BY,	GM, KG,	KE, KZ,	LS, MD,	MW, RU, GR,	MΖ, TJ,	NA, TM,	SD, AT,	SL, BE,	SZ, BG,	TZ, CH,	UG, CY,	ZM, CZ,	ZW, DE,	AM, DK,						
7) [ ]	2004	SI, SN,	SK, TD,	TR, TG	BF,	ВJ,	CF,	CG,	CI,	CM,	GA,	GN,	GQ,	GW,	ML,	MR,	NE,						
CA	2539 1663	117			A1		2005	0407		AU 2004-276337 CA 2004-2539117 EP 2004-789074						20040924							
CN.		AT, IE,	BE, SI,	CH, LT,	DE, LV,	DK, FI,	ES, RO,	FR, MK,	GB, CY,	GR, AL,	IT, TR,	LI, BG,	LU, CZ,	NL, EE,	SE, HU,	MC, PL,	PT, SK,	HR					
JP US	2008	5067 0132	85 459		T A1		2007 2008	0322 0605		CN 2004-80034571 JP 2006-528279 US 2006-574088						20040924							
	JP 2008094847 IORITY APPLN. INFO.:				A		2008	0424		US 2	003-	5058	-		20071030 P 20030924 P 20031229								
										US 2 JP 2	004- 006-	5610 5282	82P 79		P 2 A3 2	0040 0040	409 924						
THER SO	* *				CASI	REAC	T 14	2:35				WO 2004-US31591 W 20040924 CASREACT 142:355054; MARPAT 142:355054											

GΙ

AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction The inhibitory

Ι

capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium] bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC 50 values in the range of below 1 up to 20  $\mu\text{M}$ . I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

IT 603985-86-0P 603985-88-2P 603985-90-6P 603985-94-0P 603991-95-3P 603991-96-4P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amide derivs. as inhibitors of histone deacetylase)  ${\tt RN} - 603985 - 86 - 0 - {\tt CAPLUS}$ 

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

$$^{\text{HO-CH}_2}$$
  $^{\text{O}}$   $^{\text{CH}_2}$   $^{\text{N}}$   $^{\text{N}}$   $^{\text{C}}$   $^{\text{N}}$   $^{\text{C}}$   $^{\text{N}}$   $^{\text{C}}$ 

RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]- (CA INDEX NAME)

$$CH_2-CH_2$$
 $N$ 
 $N$ 
 $N$ 
 $C-NH-OH$ 
 $O$ 

RN 603985-94-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} S & CH_2-C-N & N & N \\ \hline \\ C-NH-OH \\ O & O \end{array}$$

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

6

REFERENCE COUNT:

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:300394 CAPLUS

DOCUMENT NUMBER: 142:373563

TITLE: Preparation of amide derivatives as inhibitors of

histone deacetylase

INVENTOR(S): Moradei, Oscar; Paquin, Isabelle; Leit, Silvana;

Frechette, Sylvie; Vaisburg, Arkadii; Besterman,

Jeffrey M.; Tessier, Pierre; Mallais, Tammy C.

PATENT ASSIGNEE(S): Methylgene, Inc., Can. SOURCE: PCT Int. Appl., 389 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT	KIN	D	DATE			APPL	ICAT	ION	NO.		DATE					
WO 2005	WO 2005030704						0407		 WO 2	004-	 US31	 590			 0040	
W:	ΑE,	AG,	AL,	ΑM,	ΑT,	ΑU,	ΑZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,
	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,
	GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KΕ,	KG,	KP,	KR,	KΖ,	LC,
	LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NA,	NI,
	NO,	NΖ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,
	ТJ,	TM,	TN,	TR,	ΤΤ,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW
RW:	BW,	GH,	GM,	ΚE,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,
	ΑZ,	BY,	KG,	KΖ,	MD,	RU,	ТJ,	TM,	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,
	EE,	ES,	FΙ,	FR,	GB,	GR,	HU,	ΙE,	ΙΤ,	LU,	MC,	NL,	PL,	PT,	RO,	SE,
	SI,	SK,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	GW,	${ m ML}$ ,	MR,	ΝE,
	SN,	TD,	ΤG													
JP 2008	0948	47		Α		2008	0424		JP 2	007-	2813	56		2	0071	030
PRIORITY APP	LN.	INFO	.:						US 2	003-	5058	84P		P 2	0030	924
									US 2	003-	5329	73P		P 2	0031	229
									US 2	004-	5610	82P		P 2	0040	409
								1	JP 2	006-	5282	79		A3 2	0040	924
OTHER SOURCE GI	(S):			CAS	REAC	T 14	2 <b>:</b> 37:	3563	; MA	RPAT	142	:373	563			

AB Title compds. I [Ar1 = (un)saturated-, (un)substituted-mono or fused poly-cyclic hydrocarbyl optionally containing 1-4 heteroatoms per ring; R1 = (un)substituted-mono-, -bi-, -tri-cyclic-aryl or -heteroaryl; R2, R3, and R4 independently = H, halo, amino, etc.; R5 and R6 independently = H, alkyl, aryl, etc.; x = 0-1; Y = any pharmaceutically acceptable chemical moiety consisting of 1 to 50 atoms with provisions] and their pharmaceutically acceptable salts, are prepared and disclosed as inhibitors of histone deacetylase. Thus, e.g., II was prepared by Suzuki coupling of 2-bromo-2-nitro-phenylamine (preparation given) with 2-thiopheneboronic acid followed by carbonylation with 4-[3,4-dimethoxy-(phenylamino)-methyl]benzoic acid (preparation given) and subsequent reduction The inhibitory

Ι

capability of I towards antiproliferative activity of histone deacetylase enzyme was evaluated using 3-[4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium] bromide (MTT) assay and it revealed that certain compds. of the invention had MTT IC 50 values in the range of below 1 up to 20  $\mu\text{M}$ . I as histone deacetylase inhibitors should prove useful in the treatment of diseases such as, but not limited to, cell proliferative disease, protozoal disease, and fungal disease.

IT 603985-86-0P 603985-88-2P 603985-90-6P 603985-94-0P 603991-95-3P 603991-96-4P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amide derivs. as inhibitors of histone deacetylase)  ${\tt RN} - 603985 - 86 - 0 - {\tt CAPLUS}$ 

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

$$^{\text{HO-CH}_2}$$
  $^{\text{O}}$   $^{\text{CH}_2}$   $^{\text{N}}$   $^{\text{N}}$   $^{\text{C}}$   $^{\text{N}}$   $^{\text{C}}$   $^{\text{N}}$   $^{\text{C}}$ 

RN 603985-88-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603985-90-6 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]- (CA INDEX NAME)

$$CH_2-CH_2$$
 $N$ 
 $N$ 
 $N$ 
 $C-NH-OH$ 
 $O$ 

RN 603985-94-0 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]- (CA INDEX NAME)

RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} S & CH_2-C-N & N & N \\ \hline \\ C-NH-OH \\ O & O \end{array}$$

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

6

REFERENCE COUNT:

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737723 CAPLUS

DOCUMENT NUMBER: 139:261309

TITLE: Preparation of N-hydroxy-5-piperazino(piperidino or

diazepino)-2-pyrimidinecarboxamides and N-hydroxy-4-piperazino(piperidino or

diazepino) benzamides as new inhibitors of histone

deacetylase

INVENTOR(S): Angibaud, Patrick Rene; Pilatte, Isabelle Noeelle

Constance; Van Brandt, Sven Franciscus Anna; Roux, Bruno; Ten Holte, Peter; Verdonck, Marc Gustaaf

Celine; Meerpoel, Lieven; Dyatkin, Alexey Borisovich

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 72 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

PA:						KIND DATE APPLICATION NO.												
WO									WO 2003-EP2514							0030	311	
	W:	ΑE,	AG,	AL,	AM,	AT,	AU,	ΑZ,	BA,	BE	B, BG,	BR,	BY,	BZ,	CA,	CH,	CN,	
		CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	ΕC	C, EE,	ES,	FΙ,	GB,	GD,	GE,	GH,	
		GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE	KG,	KP,	KR,	KΖ,	LC,	LK,	LR,	
		LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN	I, MW,	MX,	MZ,	NO,	NZ,	OM,	PH,	
		PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK	C, SL,	TJ,	TM,	TN,	TR,	TT,	TZ,	
		UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM	I, ZW							
	RW:										, TZ,							
		KG,	KΖ,	MD,	RU,	ΤJ,	TM,	ΑT,	BE,	BG	G, СН,	CY,	CZ,	DE,	DK,	EE,	ES,	
		FΙ,	FR,	GB,	GR,	HU,	ΙE,	ΙΤ,	LU,	MC	, NL,	PT,	RO,	SE,	SI,	SK,	TR,	
		BF,	ВJ,			CI,	CM,	GA,	GN,	GÇ	, GW,	ML,	MR,	ΝE,	SN,	TD,	ΤG	
CA	2475	764			A1		2003	0918	1	CA	2003-	-2475	764		2	0030	311	
ΑU	2003	2187.	36		A1 A1 A1		2003	0922		AU	2003-	-2187	36		20030311 20030311 20030311			
EP	1485						2004	1215		ΕP	2003-	-7119	80		2	0030	311	
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR	R, IT,	LI,	LU,	NL,	SE,	MC,	PT,	
		ΙE,	SI,	LT,	LV,						, TR,					SK		
BR	2003	0800	81		Α		2004	1221		BR	2003-	-8081			2	0030	311	
CN	1639: 1642: 5348: 2005:	125			Α		2005	0713	1	CN	2003-	-8056	75		2	0030	311	
CN	1642	551			Α		2005	0/20		CN	2003-	-8058	33		2	0030	311	
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ΙN	20041	DN02			Α		2007				2004-					0040	831	
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ИО	2004	0041	94		Α		2004	1001			2004-					0041		
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WO 2003-EP2514 W 20030311

OTHER SOURCE(S): MARPAT 139:261309

GΙ

The title compds. [I; n = 0-3; t = 0-4; Q, X, Y = N, C; Z = N, CH; R1 = AΒ CONR7R8, NHCOR9, CO(alkanediyl)SR9, etc. (wherein R7, R8 = H, OH, alkyl, etc.; R9 = H, alkyl, alkylcarbonyl, etc.); R2 = H, halo, OH, etc.; L = a bond, alkanediyl, alkanediyloxy, NH, CO, NHCO; each R3 = H and one H atom can be replaced by aryl; R4 = H, OH, NH2, etc.; A = (un)substituted Ph, cyclohexyl, pyridyl, etc.], having histone deacetylase inhibiting enzymic activity, were prepared and formulated. E.g., a multi-step synthesis of II which showed pIC50 of 5.121 against HDAC, was given.

ΙI

ΙT 603985-87-1P 603985-89-3P 603985-91-7P

603985-95-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of piperazino(piperidino or diazepino) substituted 2-pyrimidinecarbohydroxamic acids and N-hydroxybenzamides as new inhibitors of histone deacetylase)

RN 603985-87-1 CAPLUS

5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(hydroxymethyl)phenyl]-2-CN furanyl]methyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-86-0 C21 H23 N5 O4 CMF

10/513699

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-89-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylmethyl)-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-88-2 CMF C20 H21 N5 O2

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-91-7 CAPLUS

<12/04/2007>

Erich Leese

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-naphthalenyl)ethyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (5:4) (CA INDEX NAME)

CM 1

CRN 603985-90-6 CMF C21 H23 N5 O2

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 603985-95-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[[5-[4-(4-morpholinylmethyl)phenyl]-2-furanyl]methyl]-1-piperazinyl]-, 2,2,2-trifluoroacetate (1:2) (CA INDEX NAME)

CM 1

CRN 603985-94-0 CMF C25 H30 N6 O4

CM 2

CRN 76-05-1 CMF C2 H F3 O2 10/513699

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:737586 CAPLUS

DOCUMENT NUMBER: 139:261308

TITLE: Preparation of anyl and heteroaryl hydroxamic acids as

inhibitors of histone deacetylase for treating

proliferative diseases

INVENTOR(S): Van Emelen, Kristof; Verdonck, Marc Gustaaf Celine;

Van Brandt, Sven Franciscus Anna; Angibaud, Patrick Rene; Meerpoel, Lieven; Dyatkin, Alexey Borisovich

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 52 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

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OTHER SOURCE(S): MARPAT 139:261308

GΙ

$$R^{1}$$
  $Q=X$   $N$   $Z-R^{3}$   $R^{4}$ 

AΒ This invention comprises aryl and heteroaryl hydroxamic acids (shown as I; variables defined below; e.g. II) having histone deacetylase inhibiting enzymic activity; their preparation, compns. containing them and their use as a medicine. Compds. I show excellent in-vitro histone deacetylase inhibiting enzymic activity, have advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity), and show good metabolic stability and high bioavailability and more particular show oral bioavailability. They can also be used for detection and identification of histone deacetylase. General synthetic procedures and characterization data for twenty-seven I are included; also, prepns. of 12 intermediates are included. For example, a 59 % yield of 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5-carbohydroxamic acid was obtained by removing the O-tetrahydropyranyl group of its ester using trifluoroacetic acid; the ester was prepared in 61 % yield from N'-(ethylcarbonimidoyl)-N,N-dimethyl-1,3-propanediamine monohydrochloride, sodium 2-[4-(dimethylaminosulfonyl)piperazin-1-yl]pyrimidine-5carboxylate, O-(tetrahydro-2H-pyran-2-yl)hydroxylamine, and 1-hydroxy-1H-benzotriazole in CH2Cl2/THF. The sodium salt was obtained by base hydrolysis of the Et ester; the ester was prepared in 73 % yield from Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate and dimethylsulfamoyl chloride; Et 2-(piperazin-1-yl)pyrimidine-5-carboxylate was obtained in <96 % yield from Et 2-(4-benzylpiperazin-1-yl)pyrimidine-5-carboxylate by hydrogenation using Pd/C; the benzyl derivative was obtained from 1-(phenylmethyl)piperazine, (135 mL) was added gradually to a solution of potassium carbonate (0.18 mol) and 2-(methylsulfonyl)-5pyrimidinecarboxylic acid Et ester, K2CO3 in MeCN. For I: n is 0-3; Q, X and Y are N or C; Z is N or CH; R1 is -C(0)NR5R6, -N(H)C(0)R7, -C(0)-C1-6alkanediylSR7, -NR8C(0)N(OH)R7, -NR8C(0)C1-6alkanediylSR7, -NR8C(O)C:N(OH)R7 or another Zn-chelating-group; R2 is H, halo, hydroxy, amino, nitro, C1-6alkyl, C1-6alkyloxy, trifluoromethyl, di(C1-6-alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl. R3 is H, C1-6-alkyl, arylC2-6alkenediyl, furanylcarbonyl, naphthalenylcarbonyl, -C(0)phenylR9, C1-6alkylaminocarbonyl, aminosulfonyl, arylaminosulfonyl, aminosulfonylamino, di (C1-6-alkyl) aminosulfonylamino, arylaminosulfonylamino, aminosulfonylaminoC1-6-alkyl, di(C1-6alkyl)aminosulfonylaminoC1-6-alkyl, arylaminosulfonylaminoC1-6alkyl, di(C1-6-alkyl)aminoC1-6alkyl, C11-12-alkylsulfonyl, di(C1-6alkyl)aminosulfonyl, trihaloC1-6-alkylsulfonyl, di(aryl)C1-6alkylcarbonyl, thiophenylC1-6alkylcarbonyl, pyridinylcarbonyl or arylC1-6alkylcarbonyl. R4 is H, hydroxy, amino, hydroxyC1-6alkyl, C1-6alkyl, C1-6alkyloxy,

arylC1-6alkyl, aminocarbonyl, hydroxycarbonyl, aminoC1-6-alkyl, aminocarbonylC1-6-alkyl, hydroxycarbonylC1-6-alkyl, hydroxyaminocarbonyl, C1-6-alkyloxycarbonyl, C1-6-alkylaminoC1-6-alkyl or di(C1-6-alkyl)aminoC1-6-alkyl; when R3 and R4 are present on the same C atom, R3 and R4 together may form -C(0)-NH-CH2-NR10- wherein R10 is H or aryl; when R3 and R4 are present on adjacent C atoms, R3 and R4 together may form :CH-CH:CH-CH:; addnl. details are given in the claims.

IT 603991-96-4P

RL: ARG (Analytical reagent use); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

RN 603991-96-4 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

IT 603991-95-3P 603992-24-1P 603992-25-2P 603992-26-3P 603992-27-4P 603992-28-5P

RL: ARG (Analytical reagent use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate and reagent for detection/identification of histone deacetylase; preparation of aryl and heteroaryl hydroxamic acids as inhibitors of histone deacetylase for treating proliferative diseases)

RN 603991-95-3 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-24-1 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-[2-(2-thienyl)acetyl]-1-piperazinyl]- (CA INDEX NAME)

$$\begin{array}{c|c} S & CH_2-C-N & N & N \\ \hline \\ C-NH-OH \\ \hline \\ O & \\ \end{array}$$

RN 603992-25-2 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-26-3 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

RN 603992-27-4 CAPLUS

CN 5-Pyrimidinecarboxamide, 2-[4-[2-(3,4-dimethoxyphenyl)acetyl]-1-piperazinyl]-N-hydroxy- (CA INDEX NAME)

RN 603992-28-5 CAPLUS

CN 5-Pyrimidinecarboxamide, N-hydroxy-2-[4-(2-pyridinylcarbonyl)-1-piperazinyl]- (CA INDEX NAME)

REFERENCE COUNT:

6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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